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Subliminal stochastic electrical stimulation of the vestibular system: Effects on Posture and Perception

<u>PhD Thesis</u>

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Abstract

Stochastic resonance (SR) in non-linear sensory systems has been shown to improve the detection of weak, sub-threshold signals. Alongside its effects on information processing in the visual, auditory and somatosensory systems, it has recently been demonstrated also in the vestibular system. Improving the function of the latter is crucial for the treatment of patients with dizziness and instability. However, the characterization of the SR effect on the vestibulo-perceptual system, which is a vital modality for the multisensory construct of spatial orientation, is still lacking. To do that, we conducted two experiments in which we attempted to answer the following: Can SR enhance vestibulo-perceptual performance? If yes, in what frequencies of motion? Do the semicircular canals as well as the otoliths contribute to the enhancement? or it is confined to one of these structures? In the first experiment, we determined the optimal noisy galvanic vestibular stimulation (nGVS) amplitudes for 13 healthy subjects using a static posturography task. These amplitudes were then applied during vestibular direction-recognition experiments in the roll plane at 0.2, 0.5 and 1HZ. We found that nGVS significantly improved motion perception at 0.5 and 1Hz, but not at 0.2Hz. Further, the magnitude of improvements induced by the nGVS in the postural and perceptual systems was found not to be correlated. In the second experiment, given that roll-tilts activate both the SCCs and otoliths, we sought to determine the contribution of each of these structures to the enhanced perceptual performance in isolation. After determining optimal nGVS amplitudes for 12 healthy subjects during quiet standing on a force platform, these amplitudes were applied during direction recognition tasks in the inter-aural plane with the head straight (primarily otolith mediated perception), and in the yaw plane with the head pitched 71 deg (primarily SCCs-mediated perception). nGVS significantly enhanced perception during the inter-aural task in 9 of 12 subjects, while it had no significant effect on the perception during yaw rotations. Moreover, there was a significant correlation between the higher baseline vestibular thresholds, and the larger magnitude of improvement after nGVS application. Taken together, we show that nGVS enhances vestibular motion perception at behaviorally-relevant frequencies, where the main contribution to this enhancement comes from the otoliths. These results further support the use of nGVS as a rehabilitation method in patients with vestibular disorders,

with a potential complementary effect to vestibular implants that currently exclusively target SCCs-function.

2 Section 1

2.1 Introductory summary

2.1.1 Background

The vestibular system, an integral part of the labyrinth embedded in the petrous portion of the temporal bone, senses angular and linear acceleration of the head as well as tilt in relation to gravity. These actions are accomplished via the working of three Semicircular canals (SCCs) that are roughly orthogonal to each other, and two otolith organs, namely the utricle and saccule. The vestibular sensation triggers compensatory reflexive actions of the eyes, head and body when the head is in motion in order to ensure physical and perceptual stability. However, when a disruption of the vestibular function occurs due to a given pathology, debilitating symptoms of dizziness and vertigo develop, which result from the asymmetrical or reduced vestibular information received by the brain about the orientation of the head relative to the external world. Although the brain compensates for the lost/reduced vestibular function by up-regulating information coming from other sensory sources that are important for balance such as the visual and somatosensory systems, a considerable proportion of patients with vestibular disorders do not fully recover and develop a chronic form of dizziness and instability (Bisdorff et al., 2013).

In the effort to understand how the vestibular system processes information about self-motion, which is cardinal for the understanding of normal and pathological vestibular states, galvanic vestibular stimulation (GVS) has been used in this regard (Fitzpatrick and Day, 2004; Cathers et al., 2005; Schneider et al., 2009; St George and Fitzpatrick, 2011). By passing a small direct current between bipolar electrodes placed behind the ears, GVS has been demonstrated to stimulate both the vestibular hair-cells and primary afferent (Gensberger et al., 2016; Goldberg et al., 1984; Kim and Curthoys, 2004). This signal is considered by the brain as a real, unplanned head movement in space, to which the balance system consequently organizes a compensatory whole body response (i.e. contraction of specific target muscles to maintain balance and head stability) (Fitzpatrick and Day, 2004). Such a GVS-induced body response, although reflexive and stereotyped, has been revealed to be altered (i.e. different target- muscle contraction result from the same stimulation) when the head orientation is changed during stimulation (Lund and Broberg, 1983). In fact, not only postural responses change by adapting different head positions, but also the perception of self-motion has been shown to be different (Fitzpatrick and Day, 2005; St George and Fitzpatrick, 2011). For example, when pitching the head down while seated, the application of GVS induces the perception of whole body yaw rotation. However, when the head is straight, the same GVS stimulus evokes the perception of roll motion. These head-orientation-dependent changes in turn not only reflect the hard-wired nature of the sensorimotor postural control system, but also highlight the important congruity between the perception of self motion and the resultant physical responses (St George et al., 2011).

GVS stimuli have been traditionally presented as sinusoidal or square-wave currents (Peters et al., 2015; Cathers et al., 2005). In recent years, another form of GVS has been increasingly used, which is based on delivering electrical currents to the mastoid processes as zero-mean inferences, or *noise*. This noisy GVS (nGVS) stimulation has been used to study vestibular function in two main forms: 1) *sub-threshold* nGVS and 2) *supra-threshold* nGVS.

The Supra-threshold form of nGVS has been used to elucidate the transfer-function of vestibular information processing from the periphery to neck and lower limb muscles that maintain postural balance via coherency measures (Dakin et al., 2007; Dakin et al., 2010; Milan et al., 2010) (Figure 1). Supra-threshold nGVS is particularly suited for this purpose since unlike the sinusoidal and square-wave stimuli; it evokes postural responses that are free from the bias of expectancy effects (Pavlik et al., 1999). Furthermore, the acceleration signal induced by this stimulation does not produce an illusory percept of motion to a specific direction; likely because noise is considered by the brain as unreliable source of information, leading to the down-weighing of signals coming from the vestibular apparatus and the increased reliance on other sensory systems important for balance (Weech et al., 2018). In fact, the latter study has shown that applying supra-threshold nGVS to subjects while seated in a virtual environment reduces vection and motion sickness, thus providing support for the down-regulation of the noisy vestibular information in the context of vestibular perception. Thus, this feature is vital for studying vestibulo-spinal reflexes that are not induced by corrective body responses initiated by the modulation of the foot position as a result of an illusory percept of motion (Day et al., 2002).

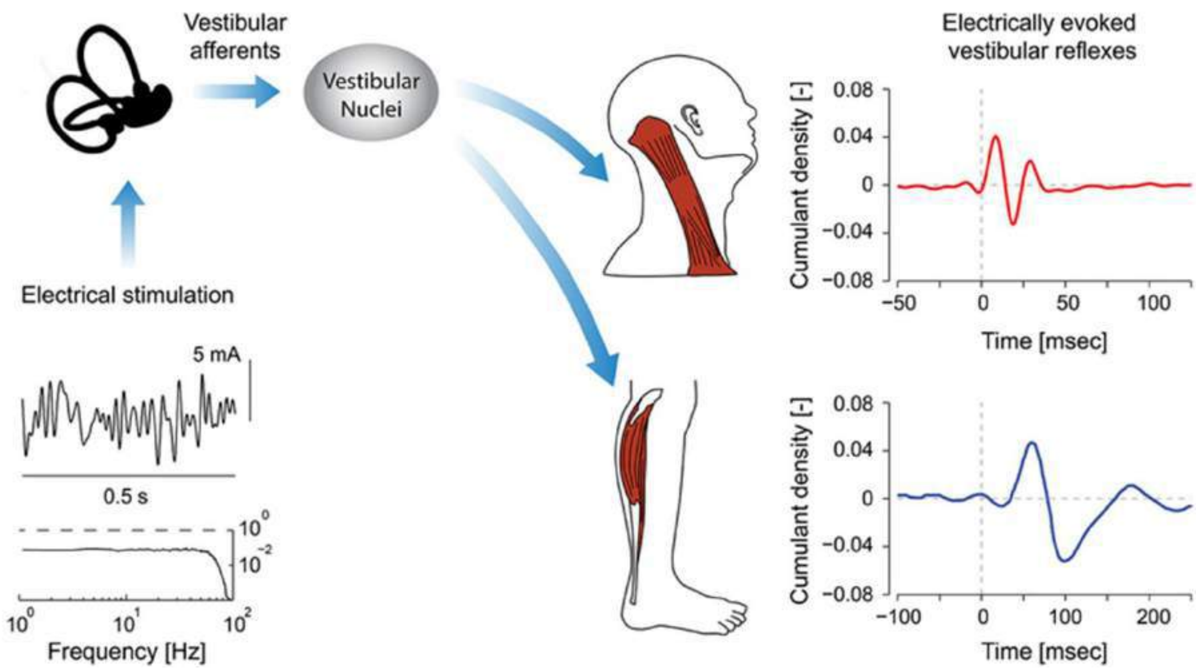

Figure 1*. *Signal processing pathways and evoked reflex responses as a result of supra-threshold nGVS. *An example of electrical stimulation (Left middle sub-figure) with a frequency bandwidth spanning 0–75 Hz (Left bottom sub-figure). When applied to the mastoids, this stimulation provokes a specific vestibular afferent activity that is conveyed to vestibulo-spinal pathways via the vestibular nuclei, reaching axial and appendicular muscles motor-neurones, finally leading to a postural response (Adapted and modified from Forbes et al., 2015).*

On the other hand, the sub-threshold form of nGVS, typically presented at amplitudes below 1mA, has been used as a method to *enhance* vestibular function. Using low-amplitude noisy currents has been demonstrated to enhance the performance of non-linear sensory systems in detecting weak, normally undetected, incoming signals (Collins et al., 1993). This change in the systems' performance is attributed to the mechanism of stochastic resonance (SR), in which weak incoming signals become enhanced and amplified beyond the information processing threshold by interacting with an additional low-intensity noise (Moss, 2004) (Figure 2). The SR-based enhancing effects have been depicted in sensory systems such as the auditory (Zeng et al., 2000), visual (Van der Groen et al., 2016), tactile (Collins et al., 1996) and more recently on the vestibular system (Iwasaki et al., 2014). Regarding the latter, it has been demonstrated that SR facilitates better performance of a range of vestibulo-reflexive functions such as vestibulo-oculomotor, posture and gait of healthy subjects as well as patients with bilateral vestibular loss (Serrador et al., 2016, Iwasaki et al., 2014; Wuehr et al., 2016a; Wuehr et al., 2016b; Mulavara et al., 2015; Iwasaki et al., 2017). However, while the *perception* of vestibular signals induced by other forms of GVS stimuli is well documented, the perception of the sub-threshold nGVS is difficult to assess because of its noisy and low-intensity nature. Further, unlike other forms of GVS, it is not the perception of the nGVS-induced signal itself that is important in the case of this low-intensity nGVS; rather, it is the perception of the weak physiologic (e.g. motion) signal that presumably gets amplified by the presence of this noise that is crucial to examine whether it gets manifested perceptually. Investigating this relationship is especially important since vestibular perception forms the cornerstone of the cognitive construct of dizziness; which means that if the low-intensity nGVS proves efficient in facilitating better information processing in vestibular perception similarly to the vestibulo-reflexive functions, it can potentially be rendered as a rehabilitation tool that improves the signs and symptoms of patients with dizziness. A support for the potential effect of SR on higher-order vestibular function was reported by Kim et al., 2013 who found that stochastic galvanic stimulation alters the modulation of synchrony patterns of EEG frequency bands, which may reflect the enhancement of neural information processing.

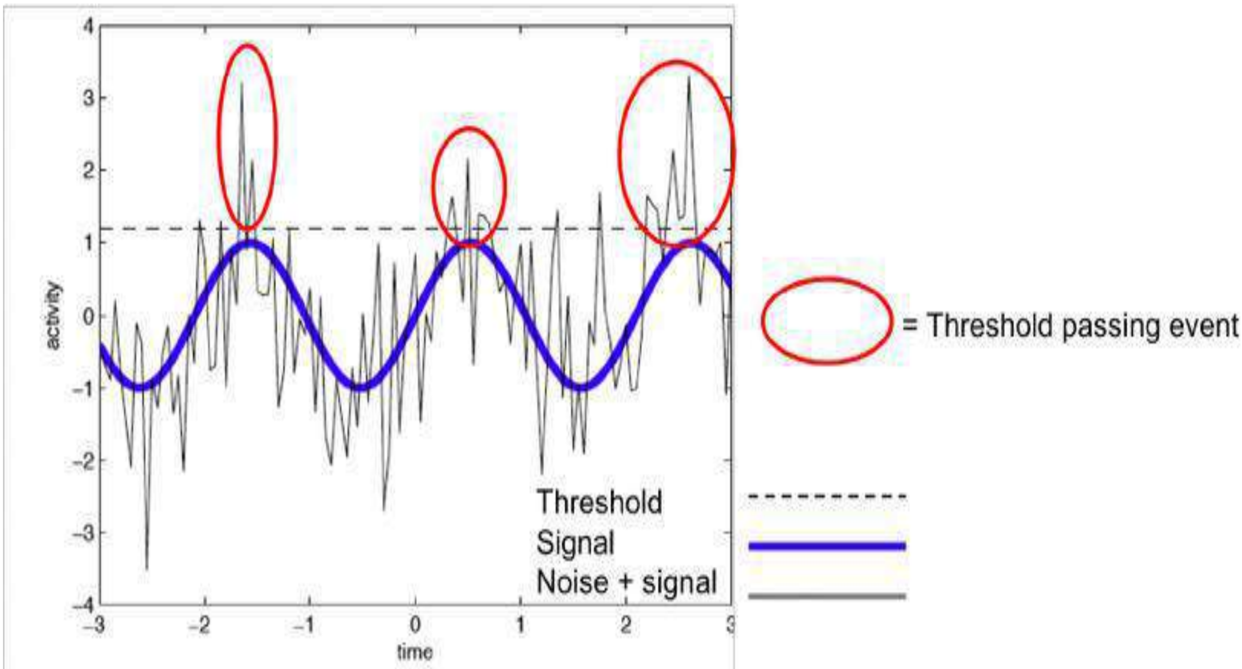

Figure 2. Stochastic Resonance. *The blue line represents the sub-threshold incoming sensory signal, which does not reach the detection threshold of the sensory system (dotted line). Via the interaction with a specified amount of noise (grey line), the low-intensity signal becomes amplified beyond the threshold (red circles) and an action potential is triggered carrying the sub-threshold signal. (Adapted from Söderlund and Sikström, 2008)*

2.1.2 Experimental studies

In order to elucidate and characterize the effect of nGVS on vestibular motion perception, we conducted two studies in which we aimed to answer the following questions:

1- Can nGVS enhance vestibular motion perception? If yes, in what frequencies of motion?

2- Can the improvement observed, if any, be attributed to the whole vestibular system or is it confined to specific components in the vestibular apparatus?

In the following I present a short summary of the two performed studies.

2.1.3 Study 1- Summary

Background

In this study we investigated whether roll-tilt vestibular motion perception can be improved by the same nGVS amplitudes that enhance postural performance. To optimize our measurement parameters, we initially needed to ensure that the nGVS signal bandwidth actually covers the natural sway-frequency bandwidth of healthy subjects during a quiet-standing task on foam with eyes closed (i.e. the postural task of the study). This step did not only inform us about the frequency bandwidth of the nGVS we needed to use during the postural task, but also about the frequencies that should be tested during the vestibular-perceptual tasks. To do that, a device with inertial sensors (EyeSeeCam, Munich, Germany) was placed on the heads of two healthy subjects whilst performing a quiet stance task on foam for 30 seconds with eyes closed using a force platform. Power analysis revealed that the predominant sway-frequencies ranged between 0-2Hz. Consequently, the nGVS frequency-bandwidth was set to 0-2Hz, whereas the roll-tilt frequencies to be tested for the perceptual task were set at 0.2, 0.5 and 1Hz, all of which fell within the bandwidth of the stimulation signal.

Methods

13 healthy subjects performed a quiet-standing task on foam with eyes closed for 30s using a force-platform. This procedure was repeated eight times, while on each time, one of eight different nGVS amplitudes (0-700 uA) was presented in random order to find the intensity that optimally reduces sway. The optimal nGVS amplitude was defined as the amplitude at which at least two of three stance parameters, namely the mean velocity (MV), the envelopment area under the trace and the root-mean square (RMS) of the center-of-pressure displacements, improved better than the baseline measure (i.e. 0uA). After determining the optimal nGVS amplitude for each subject, these optimal amplitudes were then applied during a roll-tilt vestibular direction-recognition task to assess their impact on the vestibulo-perceptual function. Using a 6-degree-of-freedom motion platform (Moog 6DOF2000E, East Aurora, New York), the direction-recognition task was composed of single cycle tilts either to the right or to the left following a raised cosine velocity profile (Figure 3) and subjects had to indicate by a button-press whether they perceived the movement to

the right or to the left. Three different roll-tilt frequencies were tested, namely 0.2, 0.5 and 1Hz, each performed once with sham, and once with the optimal nGVS amplitude. Each block consisted of 150-trials, using the 3-down 1-up psychophysical criteria. A cumulative Gaussian distribution function was then fitted to the response data, which yielded a maximum likelihood psychometric fit. All conditions were performed in a randomized order for nGVS and sham stimulation (i.e., nGVS at 0μA). Noise-cancelling head-phones were used to mask incoming sound cues from the platform. All experiments were performed in total darkness with eyes closed.

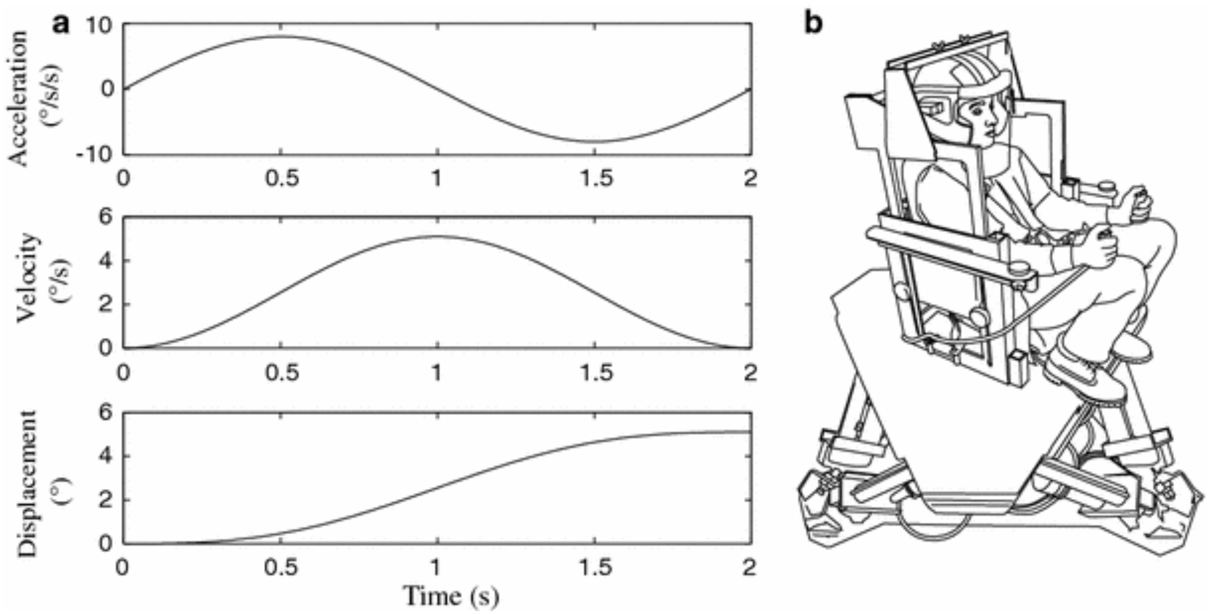

***Figure3**. **Example of motion stimulus and experimental set-up**. **a**) Illustration of acceleration (top), velocity (middle) and displacement (bottom) for a given motion stimulus. Motion stimuli consisted of single cycles of sinusoidal acceleration (example frequency is 0.5Hz). **b)** Schematic illustration of the experimental set-up. Each subject was*

securely seated in a chair that was mounted on the motion platform (Moog 6DOF2000E). (Adapted and modified from Grabherr et al., 2008)

Results

Compared to sham trials, the application of nGVS significantly enhanced direction recognition during roll tilts at 0.5 Hz ($F_{1,12}$ = 5.006, p = 0.045; mean threshold reduction: 14.1 ± 0.5%). and 1Hz ($F_{1,12}$ = 8.455, p = 0.013; mean threshold reduction: 20.1 ± 0.5%) , but not during 0.2Hz. Interestingly, we found no correlation between the magnitude of improvements of nGVS during the stance task and the motion-perception task. These results suggest that nGVS exerts an SR effect on vestibular motion perception; most likely by influencing information processing in the peripheral vestibular organ, which then influences central vestibular functions.

2.1.4 Study 2 – Summary

Background

As we have demonstrated in study 1, nGVS enhances vestibular motion perception during roll tilts at 0.5 and 1Hz. An important question remained unanswered: Given that roll tilts activate both the SCCs and otolith organs, does the whole vestibular apparatus contribute to the improvement induced by nGVS? Answering this question is crucial since investigating the nGVS's anatomical site of action provides a deeper insight into its working mechanisms, which in turn yields better-informed intervention strategies for patients.

GVS research has shown that both the SCCs and otolith organs are affected by the electrical signal (Goldberg et al., 1984). However, it has also been revealed that when using GVS currents at low amplitude, vestibular activation is predominated by the otolith irregular afferents (Zink et al., 1998; Kim and Curthoys, 2004). Given that the SR-inducing nGVS is low-amplitude by nature, it is therefore expected that nGVS would preferentially evoke otolith responses, with a potential spread into the SCCs.

But how isolating the contribution of the SCCs and otoliths to motion perception can be achieved? Previous studies have demonstrated that GVS induces a vestibular signal that is the same irrespective of the head orientation. Nonetheless, although the vestibular signal is the same, the *perception* of this signal changes with changing the orientation of the head; because the SCCs and otoliths produce vestibular signals that are referenced to a cranio-centric coordinate frame (Lund and Broberg, 1983). For example, passing currents while the head is straight-ahead produces an illusory percept of movement in the roll plane. This perception changes when the head is pitched down, where the same GVS-induced signal is now perceived as whole-body yaw rotation. Hence, when the head is pitched down, whether applying a physical rotation in the yaw plane or applying GVS while stationary, would evoke a similar perception, one that results with near zero contribution of the otoliths. Thus, the neural processes feeding orientation and self-motion perception seem to perform the equivalent of calculating the dot product of the head rotation vector and the gravitational unit vector (Day and Fitzpatrick, 2005) (figure 4)

Therefore, given that nGVS does not induce motion percept, it is possible to apply nGVS during whole body movements while the head orientation is consistent with either otoliths or SCC mediated perception. Any improvement in performance could then be regarded to the action of SR on the respective vestibular structure.

Methods

12 healthy subjects were recruited for this study. Similar to Study 1, optimal nGVS amplitudes for each subject was determined using a quiet-standing task on foam with eyes closed using a force-platform. The aim of this study was to differentiate the effect of nGVS on the SCCs and otoliths using different head orientations. The procedure of determining the optimal nGVS was therefore repeated twice, once with the head straight-ahead and once with the head pitched down by around 71 deg. The resultant optimal nGVS for each head orientation (if different from that of the other head orientation) was subsequently used when performing the direction-recognition task so to ensure comparability between the postural and perceptual tasks.

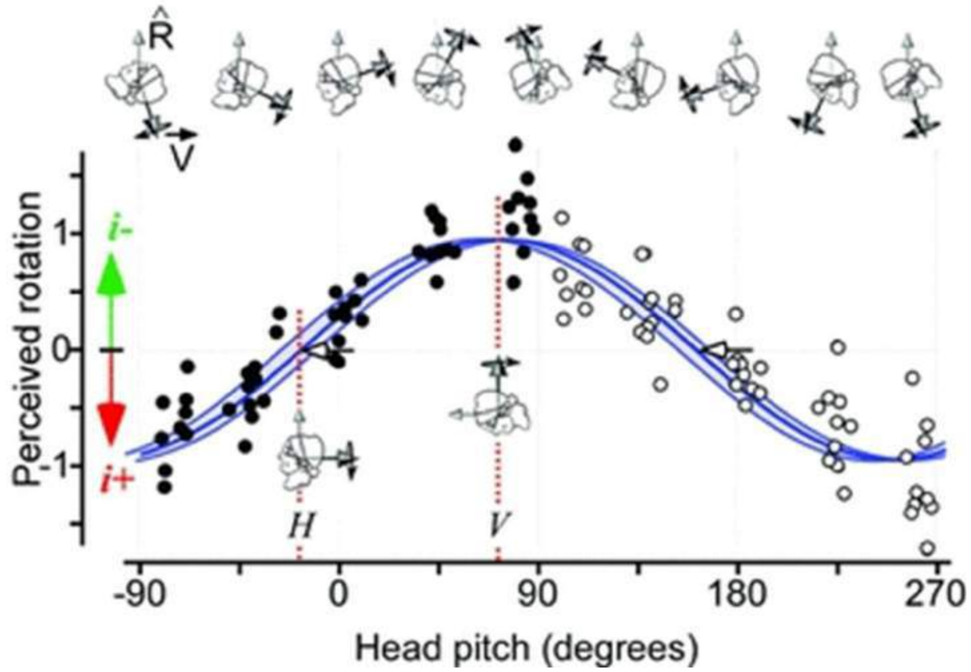

***Figure 4. Perceived rotation in normalised units for binaural bipolar galvanic stimuli with the head at different angles of pitch with least-squares sinusoidal fit**. Shaded, between the blue lines is the 95% confidence interval of the anatomical prediction. The head angles at which the vestibular stimulus produces no perception of rotation are shown by two white arrows (adapted and modified from Fitzpatrick and Day, 2015).*

After ascertaining the optimal nGVS amplitudes, subjects performed direction-recognition experiments (150 trials each, 3-down 1-up paradigm) using a 6-degree-of-freedom motion platform (Moog 6DOF2000E, East Aurora, New York) in two conditions to examine nGVS effect on otolith- and SCC-mediated vestibular perception in isolation: (A) head in normal position during inter-aural translations (otolith-mediated perception) at 1Hz and (B) head pitched forward around 71 deg during yaw rotations (SCC-mediated perception) at 1Hz. During the whole procedure, the head was stabilized by padded metal-arms attached to the subject's head. Each trial consisted of a single half-cycle that follows a raised-cosine velocity profile to the right or to the left and subjects had to indicate the direction of movement by a button press. A cumulative Gaussian distribution function was then fitted to the response data, which yielded a maximum likelihood psychometric fit. Both conditions were performed in a randomized order for nGVS and sham stimulation (i.e., nGVS at 0μA). Noise-cancelling head-phones were used to mask incoming sound cues from the platform. All experiments were performed in total darkness with eyes closed.

Results

During the postural tasks for determining the optimal nGVS amplitudes, there was no significant difference between the optimal nGVS amplitudes obtained for both head orientations (head straight-ahead and head pitched down) ($t(11) = 1.97$; $p > 0.05$; cohen's d = 0.6). In the direction-recognition tasks, for condition A (inter-aural translation), 9 out of 12 subjects showed improved recognition thresholds during nGVS compared to the sham stimulation (mean reduction=38.8±0.5%; $t(11) = 2.62$; $p \leq 0.03$; cohen's d = 0.8). Furthermore, greater nGVS-induced threshold reductions in the inter-aural task were correlated with higher baseline perceptual thresholds determined during sham stimulation ($R = -0.72$; $p \leq 0.010$). For condition B (yaw rotation, head pitched down), 6 out of 12 subjects showed mild nGVS-induced improvements, yet the group effect was not significant ($t(11) = 0.04$; $p > 0.05$; cohen's d = 0.0). No correlation was found between the magnitude of nGVS-induced threshold changes and vestibular thresholds at baseline. Finally, we did not find a correlation between noise-induced improvements in the postural and perceptual tasks.

2. Section 2

2.1. Article 1

frontiers in Neurology

ORIGINAL RESEARCH
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Noisy Galvanic Stimulation Improves Roll-Tilt Vestibular Perception in Healthy Subjects

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It has recently been demonstrated that noisy galvanic vestibular stimulation (nGVS) delivered as imperceptible white noise can improve balance control *via* the induction of stochastic resonance. However, it is unclear whether these balance improvements are accompanied by simultaneous enhancement to vestibular motion perception. In this study, 15 healthy subjects performed 8 quiet-stance tasks on foam with eyes closed at 8 different nGVS amplitudes ranging from 0 mA (baseline) to 0.5 mA. The nGVS amplitude that improved balance performance most compared to baseline was assigned as the optimal nGVS amplitude. Optimal nGVS amplitudes could be determined for 13 out of 15 subjects, who were included in the subsequent experimental procedures. The effect of nGVS delivered at the determined optimal intensity on vestibular perceptual thresholds was examined using direction-recognition tasks on a motion platform, testing roll rotations at 0.2, 0.5, and 1.0 Hz, both with active and sham nGVS stimulations. nGVS significantly reduced direction-recognition thresholds compared to the sham condition at 0.5 and 1.0 Hz, while no significant effect of nGVS was found at 0.2 Hz. Interestingly, no correlation was found between nGVS-induced improvements in balance control and vestibular motion perception at 0.5 and 1 Hz, which may suggest different mechanisms by which nGVS affects both modalities. For the first time, we show that nGVS can enhance roll vestibular motion perception. The outcomes of this study are likely to be relevant for the potential therapeutic use of nGVS in patients with balance problems.

Keywords: vestibular motion perception, noisy galvanic stimulation, stochastic resonance, vertigo, balance control

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INTRODUCTION

It is commonly thought that the presence of noise in sensory systems has detrimental effects on the system's ability to detect and process incoming signals. There is, however, growing evidence that under certain conditions an appropriate amount of noise can improve the signal-to-noise ratio in nonlinear systems and thereby enhance the recognition and transmission of the incoming information flow (1, 2). This phenomenon is based on a mechanism known as stochastic resonance (SR) in which the response of a nonlinear system to weak input signals can be optimized by the presence of a particular non-zero level of stochastic interference, i.e., noise (3). Dynamics consistent with this SR-mechanism have been demonstrated experimentally in human psychophysical studies on tactile sensation, auditory, and visual perception (4–6). Accordingly, external noise stimulation in these systems yields an improved processing of weak, sub-threshold stimuli, and thereby effectively lowers the system's recognition threshold.

Recently, several studies examined the occurrence of SR-phenomena in the human vestibular system by means of galvanic vestibular stimulation (GVS). GVS is a technique to induce neural activity in vestibular afferents (semicircular canal and otolith afferents) and has been used to investigate vestibular functions for decades (e.g., vestibulo-spinal control of posture and locomotion; vestibulo-ocular control of eye movements) (7, 8). Using zero-mean white noisy GVS (nGVS) delivered at a low imperceptible intensity during static posturography, Iwasaki and colleagues observed a consistent improvement of body balance in healthy subjects as well as in patients with a bilateral vestibular hypofunction (BVH) (9, 10). Subsequently, nGVS was also found to effectively improve dynamic balance control during walking in healthy subjects and patients with BVH (11–13). Furthermore, nGVS was shown to enhance postural and motor performance in the elderly (14), as well as in patients with Parkinson's disease (15, 16), and other neurodegenerative disorders (17). These beneficial effects of nGVS on static and dynamic body balance regulation were attributed to a noise-induced facilitation of vestibulo-spinal reflex function (18).

While there is now first evidence for nGVS-induced improvements in vestibular reflex functions, a possible parallel impact on the vestibulo-perceptual function remains to be determined. This could be particularly important for patients with BVH as they typically suffer from highly elevated perceptual thresholds in all motion planes (19). There is further evidence that human balance regulation in particular during unstable postural conditions not only requires accurate vestibulo-spinal reflex operation, but also significantly relies on vestibulo-perceptual capacities (20). Thus, the aim of this study was to examine whether nGVS effects on vestibulo-spinal function are accompanied by alterations in vestibulo-perceptual function. To this end, we (1) initially determined the individual nGVS intensity at which static balance performance of healthy participants improved optimally and (2) subsequently examined whether nGVS at the same intensity also affects vestibular perceptual function in a psychophysical direction-recognition task.

MATERIALS AND METHODS

Fifteen healthy subjects (seven females; mean age 25.1 ± 1.7 years) participated in the study. None of the participants reported any auditory, vestibular, neurologic, cardio-vascular, or other health impairments. All participants gave their written informed consent prior to the experiment. The study protocol was approved by the ethics committee of the medical faculty of the Ludwig-Maximilian University of Munich. The study was conducted in conformity with the Declaration of Helsinki.

Galvanic Vestibular Stimulation

Galvanic vestibular stimulation was delivered through 4.0 cm × 6.4 cm electrodes (Axelgaard Manufacturing, Fallbrook, CA, USA) centered over the mastoid processes behind both ears. The skin surface was cleaned and dried and a layer of electrode gel was applied before electrode placement to achieve uniform current density and minimize any irritation to the skin due to stimulation. The impedance between the electrodes was confirmed to be less than 1 kΩ. Digital signals were generated using MATLAB and converted to analog signals *via* an NI USB-6221 data acquisition device (National Instruments, TX, USA). The analog command voltage signals were subsequently passed to a constant current stimulator (DS5, Digitimer, Hertfordshire, UK), which was connected to the stimulating electrodes. The stochastic signal consisted of zero-mean Gaussian white noise (nGVS) within a frequency range of 0–2 Hz (**Figure 1B**) (21). This bandwidth was chosen to cover the frequency range of head motion occurring during quiet stance as determined in two participants using a head fixed inertial sensor (EyeSeeCam, Munich, Germany) during standing with eyes closed on foam for 30 s (**Figure 1A**).

Procedures

A common difficulty in interpreting results from SR studies is separating statistical variation from actual performance improvement at the optimal stimulus level. To avoid this issue, and due

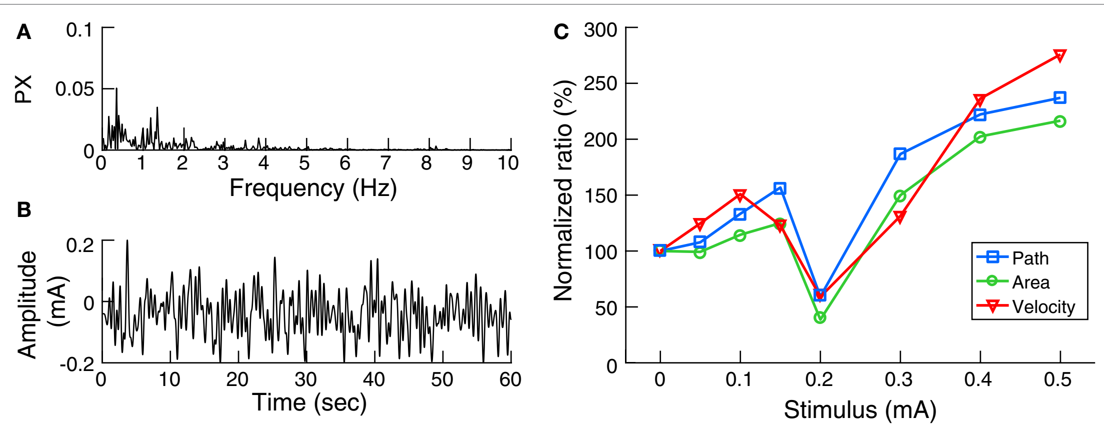

FIGURE 1 | Noisy galvanic vestibular stimulation (nGVS) characteristics and effects on postural sway: **(A)** The power spectrum (PX) of head angular velocity in the medio-lateral axis of an individual subject. **(B)** Exemplary waveform of nGVS at 0.2 mA intensity. **(C)** The nGVS balance responses of a sample subject showing lower normalized ratios of the three postural parameters tested at 0.2 mA compared to baseline.

to the combined involvement of vestibulo-spinal and vestibulo-perceptual functions in maintaining upright posture (20), this study used a two-step experimental design, in which the optimal nGVS amplitude was first determined in a postural task and the same stimulus amplitude was then used for the vestibular motion perception tasks.

Initially, for each participant, the optimal nGVS intensity was determined during a 30 s stance trial on foam with eyes closed using a stabilometer platform (Kistler 9261 A, Kistler Group, Winterthur, Switzerland). Each participant performed eight stance trials with different nGVS peak amplitudes of 0 (i.e., baseline), 50, 100, 150, 200, 300, 400, and 500 µA presented in a pseudo-random order. Between trials, subjects had a 1 min break to alleviate any after-effects of the stimulation. Three body sway measures were recorded (9): the mean velocity of the center of pressure (COP) movement (i.e., the total distance traveled by the COP over time), the envelopment area traced by the movement of the COP, and the root mean square of the COP movement. Analysis of these parameters (except area, which is computed in 2D space) was carried out in the medio-lateral plane, since bipolar vestibular electrical stimulation has been shown to induce body sway primarily in this direction (22). The ratio of each parameter during the stimulation condition to that of the baseline condition was calculated. A reduction in the normalized values of these sway parameters indicates an improvement in postural control. The optimal nGVS intensity was then determined as the one at which balance measured during the stimulus condition was simultaneously smaller than that at baseline in at least two of the three COP parameters (**Figure 1C**).

After determining each participant's optimal nGVS amplitude, subjects performed six direction-recognition experiments using a 6-degree of freedom motion platforms (Moog© 6DOF2000E, East Aurora, New York). Subjects were seated on a padded racing chair mounted on the motion platform. The head was rested on an inflatable padded pillow that adjusts itself to the actual head shape and was stabilized by placing large padded metal arms to fixate the subject's head from both sides. These arms are an extension of larger 3-degree of freedom metal arms, which are firmly connected to the metal-bar structure supporting the chair of the platform. Noise-canceling headphones were then placed over the subjects' ears to mask sound cues produced by the motion platform during the experiment. A two-buttoned (right and left) response box was handed to the subjects so that they could provide answers for the psychophysical task. Subjects' eyes were covered by designated dark glasses to remove vision and all experiments were performed in darkness.

The vestibular perception thresholds of each participant were tested in the roll plane at three different frequencies: 0.2, 0.5, and 1.0 Hz, once with active nGVS stimulation and once with sham nGVS stimulation (i.e., electrodes and stimulator in place, but no stimulation delivered). The roll plane was specifically analyzed as literature has shown that galvanic stimulation produces sensation of rotation along this axis (23). The conditions were tested in a randomized order and participants were blinded to the stimulation protocol. Each experiment consisted of 150 trials, and thresholds were determined using the three-down one-up paradigm, which converges on the 79% correct threshold (24, 25). Each trial consisted of a single half-cycle that follows a raised-cosine profile to the right or to the left and subjects had to indicate the direction of movement by a button press (26, 27). A cumulative Gaussian distribution function was then fitted to the response data, which yielded a maximum likelihood psychometric fit (28). Similar to prior studies (29, 30), we have used a direction-recognition task to minimize the influence of vibration and other non-directional cues on vestibulo-perceptual thresholds.

Outcome Measures

The primary outcome measure used in this study was the change in perceptual thresholds between the nGVS and sham conditions at the three frequencies tested. The secondary outcome analysis investigated possible correlations between improvements in the postural and perceptual performances.

Statistical Analysis

Statistical analysis was performed on participants who showed an optimal nGVS response during the static posturography task. Descriptive statistics are presented as mean ± SD. Analysis of distribution of the recorded perceptual thresholds with the Kolmogorov–Smirnov test revealed significant departures from Gaussian distributions, which is in line with previous studies using comparable procedures (31, 32). However, none of the tested conditions revealed a significant departure from a normal distribution after velocity thresholds were expressed in logarithmic units, in accordance with previous studies (27, 29, 31, 32). Effects of nGVS on log-transformed motion perception thresholds were examined using a two-way repeated measures analysis of variance (ANOVA) with the factors condition (sham vs. nGVS) and frequency (0.2, 0.5, and 1 Hz) specified. Bonferroni *post hoc* analysis was employed to correct multiple testing. Pearson's correlations were used to examine whether any significant relationship exists between the nGVS-induced improvements in balance performance and vestibular motion perception. Results were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS (version 21.0, IBM Corp., USA).

RESULTS

For 13 out of 15 participants (six females, mean age = 25.7 ± 1.4 years), we found an optimal nGVS intensity at which static body balance effectively improved compared to the baseline trial. The two subjects who did not show this postural improvement could not be further subjected to the perceptual experiments. **Table 1** presents the optimal nGVS levels determined for each of the 13 participants, together with the resultant effect on the three stance parameters analyzed.

In the motion perception paradigm, the thresholds for the sham condition were in the range of previously published literature (29, 31). There was a significant main effect of nGVS on motion perception thresholds for the factor "condition" (i.e., sham

TABLE 1 | The optimal noisy galvanic vestibular stimulation (nGVS) amplitude of each subject and its effect on the three sway parameters in the medio-lateral plane are shown.

Subject	Optimal nGVS (μA)	Area (%)	Velocity (%)	Path (%)
1	100	−45.8	−8.1	−55.4
2	50	+10	−10.7	−17.4
3	150	−18.3	−3	−18.1
4	200	−50.3	−46.8	−42.7
5	100	−59.5	−12.9	−72.7
6	100	−7	−23.2	+3.7
7	50	−65.4	−32.7	+12.2
8	200	+4	−9.5	−67.8
9	150	−42.1	+18.8	−64.7
10	200	−22.7	+7.8	−34.4
11	100	−50.2	−28	+23
12	300	−72.3	−20.7	−11.5
13	50	−27.7	−34.1	+10.8
Mean	134.6 ± 86.3	−41.9 ± 20.6	−20.8 ± 13.4	−42.7 ± 23

(−) signifies improvement and (+) signifies deterioration compared to baseline (0 μA).

vs. nGVS) (ANOVA, $F_{1,12} = 7.406$, $p = 0.019$), while no significant effect was found for the factor frequency (ANOVA, $F_{2,11} = 1.323$, $p = 0.302$). The interaction between the factors frequency and condition was, however, significant (ANOVA, $F_{2,11} = 5.269$, $p = 0.020$.). Analysis for individual frequencies revealed reduced motion perception thresholds in the nGVS condition compared to the sham condition for the 1 Hz roll motion ($F_{1,12} = 8.455$, $p = 0.013$; 0.56 vs. 0.76 deg/s, respectively; mean threshold reduction: 20.1 ± 0.5%). Similar results were also obtained for 0.5 Hz ($F_{1,12} = 5.006$, $p = 0.045$; 0.49 vs. 0.66 deg/s, respectively; mean threshold reduction: 14.1 ± 0.5%). For the 0.2 Hz condition only 3 out of 13 subjects showed a threshold reduction due to nGVS application ($F_{1,12} = 1.408$, $p = 0.25$, 0.70 vs.0.60 deg/s, respectively; mean threshold increase 9 ± 0.6%) (**Figure 2**).

No significant correlations were found between any of the improved body sway parameters and enhanced vestibular recognition thresholds at 0.5 and 1 Hz (**Figure 3**).

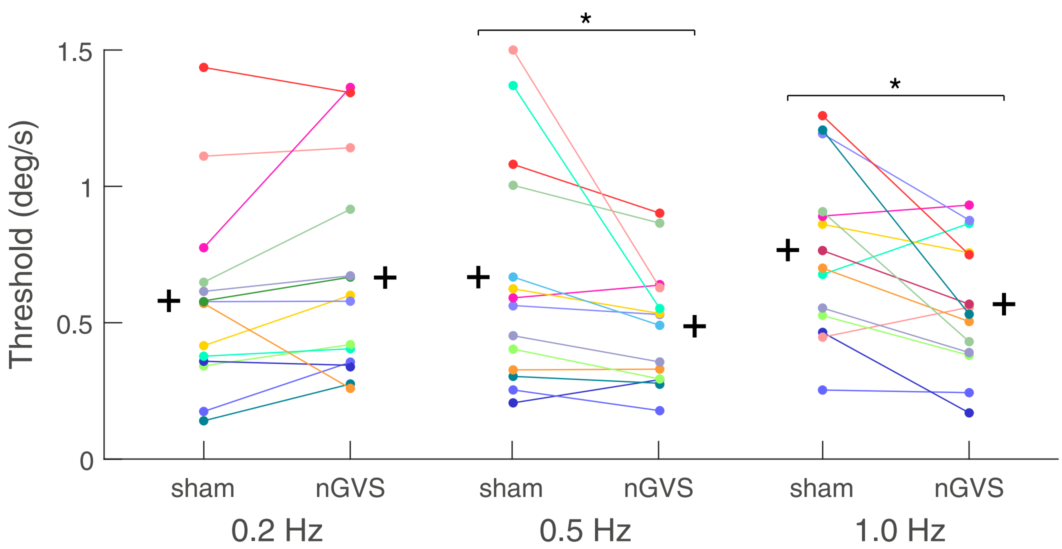

FIGURE 2 | Motion recognition thresholds for the sham and noisy galvanic vestibular stimulation (nGVS) conditions for individual subjects: a significant nGVS-induced reduction in motion recognition thresholds was found at 0.5 and 1.0 Hz. nGVS did not affect motion recognition thresholds at 0.2 Hz. The (+) sign represents the group mean of each condition tested.

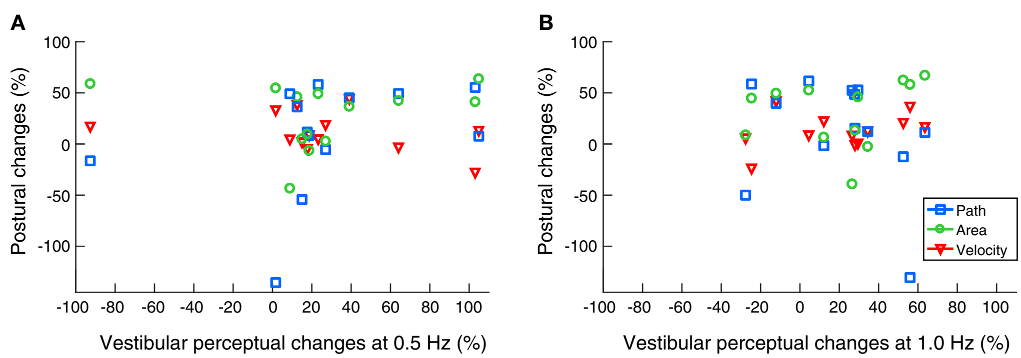

FIGURE 3 | Scatter plots on noisy galvanic vestibular stimulation-induced improvements on body balance and vestibular motion perception. No significant correlations were found between the beneficial effects on posture and vestibular recognition thresholds at 0.5 Hz **(A)** and 1.0 Hz **(B)**.

DISCUSSION

In this study, we show that nGVS not only improves stance performance in a static posturography paradigm (i.e., vestibulo-spinal function), but also influences vestibular perception in roll during a motion recognition task. Our results demonstrate that nGVS amplitudes, which enhance postural control, can also improve vestibular motion perception during roll rotations at 0.5 and 1.0 Hz, but not at 0.2 Hz. However, we did not observe any correlation between the nGVS-induced improvements during the static posturography task and their perceptual counterparts at 0.5 and 1.0 Hz.

Beneficial effects of nGVS on vestibular motion perception depended on the frequency of the roll-tilt stimulation, being effective at 0.5 and 1.0 Hz, but not at 0.2 Hz. Vestibulo-perceptual responses to roll-tilt stimulation have been characterized across a wide range of behaviorally relevant frequencies (29, 31–33). However, since roll-tilts activate both, the semicircular canals (SCCs) and otoliths, these studies do not provide answers concerning the relative contribution of these structures to the perception of roll tilts as a function of frequency. One such study has recently been published (34). It was found that motion perception thresholds for roll tilts at 0.5 and 1.0 Hz are predominantly determined by cues from the SCCs, while roll-tilt thresholds at 0.2 Hz include a substantial contribution from the otolith organs. This might explain the observed frequency dependence of nGVS on vestibular motion perception. Accordingly, the observed enhancements in vestibular perception at 0.5 and 1.0 Hz might predominantly reflect SR-enhanced signals from the SCCs. On the other hand, the presumed SR effect on roll-tilt perception at 0.2 Hz may be overridden by vector-cancelation taking place in the utricle during GVS stimulation (8).

Another outcome of our experiments was the apparent lack of correlation between improvements in the vestibulo-perceptual and vestibulo-spinal systems, both of which play an important role in the maintenance of upright postural stability (20). A possible contributing factor to this outcome could be the bandwidth of the stochastic vestibular stimulus we used in our study (0–2 Hz). Although this stimulation bandwidth has been previously validated to have high coherence with the frequencies governing postural sway responses in humans (21, 22), it did not show high coherence with responses of the lower limb and neck muscles (35, 36), both of which respond better at higher frequency bandwidths (0–20 and 0–70 Hz, respectively). Therefore, it could be possible that broader frequency bandwidths of stimulation, if also effective on vestibular perception, could, therefore, have more correlated outcomes with postural responses. Alternatively, the relative lack of correlation between nGVS effects on posture and perception may reflect a partial disassociation in processing vestibular cues along vestibulo-spinal and vestibular perceptual pathways; analogous to previous reports comparing vestibular cue processing between the vestibulo-ocular and vestibulo-perceptual systems (37, 38).

The outcomes we report in our study suggest that enhancements in balance control due to SR (11, 12). are likely to be accompanied by simultaneous perceptual improvements. Therefore, the potential implication for nGVS as a rehabilitation tool for patients with BVH could be paramount. This stems from the fact that patients with BVH suffer from highly elevated vestibulo-perceptual thresholds in all rotational and translational planes (19). Although nGVS improved vestibulo-spinal and vestibulo-perception differentially, the fact that both are actually enhanced by the same stimulation amplitude is highly important. This indicates that the same nGVS amplitude might be able to enhance both reflexive and perceptual performance of patients, regardless to the degree of enhancement it produces in each modality. Furthermore, both systems appear to be required to stabilize upright posture (20). Currently, the therapeutic regime in individuals with BVH is limited to physical therapy (39), where approximately only half of these patients benefit from this kind of intervention (40). The findings we report in this study, together with previous reports on nGVS-induced improvements in balance control as well as ocular-motor function (41) can promote an alternative or additional therapeutic option for reducing the postural imbalance and incidence of falls in this population.

Nevertheless, our study has some limitations. First, due to the lengthy testing time (4 h on average per participant), we chose only to investigate the effect of nGVS on vestibular perceptual performance in the roll plane, while not examining the other rotational and translational axes. Therefore, the improvements we show in this study may not necessarily hold true for other rotational and translational planes. Second, the frequency range for vestibular motion perception we tested was limited to the low-mid range, which may not fully encompass the frequency range of natural head motions during daily ambulation (around 0.5–5 Hz) (42). Third, our study had a relatively small sample size and the perceptual responses to stimulation exhibited by the study subjects were highly individual. This might be attributed to individual differences in inner ear anatomy, bone density, and possibly alteration in alertness to the perceptual task (although the latter is accounted for in the threshold calculation algorithm). Therefore, the current findings have to be confirmed in future on a larger study cohort.

In summary, we present here a first evidence for the sensitizing effect of nGVS on vestibular motion perception in healthy subjects. The results of this study could be a trigger to design therapeutic studies that use both the effects on balance control and on vestibular motion perception to improve mobility and quality of life in vestibular patients.

ETHICS STATEMENT

The study protocol was approved by the ethics committee of the medical faculty of the Ludwig-Maximilian University of Munich. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AK: concept, design, programming experiments, data collection, data analysis, creating **Figures 1–3**, and writing of manuscript. MW: concept, design, Matlab codes for stance performance analysis, data analysis, editing **Figures 1–3**, and review of manuscript.

CP: programming the nGVS stimulation paradigm, data analysis, and review of manuscript. KJ: concept, design, review, and amendment of manuscript. All authors have approved the final version of the manuscript and are agreed to be accountable for all aspects of the work.

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REFERENCES

1. Collins J, Chow C, Imhoff T. Stochastic resonance without tuning. *Nature* (1995) 376:236–8. doi:10.1038/376236a0
2. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. *Neurophysiol Clin* (2004) 115:267–81. doi:10.1016/j.clinph.2003.09.014
3. Benzi R, Sutera A, Vulpiani A. The mechanism of stochastic resonance. *J Phys A Math Gen* (1981) 14:L453–7. doi:10.1088/0305-4470/14/11/006
4. Collins J, Imhoff T, Grigg P. Noise-enhanced tactile sensation. *Nature* (1996) 383:770. doi:10.1038/383770a0
5. Zeng F, Fu Q, Morse R. Human hearing enhanced by noise. *Brain Res* (2000) 869:251–225. doi:10.1016/s0006-8993(00)02475-6
6. Van der Groen O, Wenderoth N. Transcranial random noise stimulation of visual cortex: stochastic resonance enhances central mechanisms of perception. *J Neurosci* (2016) 36:5289–98. doi:10.1523/jneurosci.4519-15.2016
7. Goldberg J, Smith C, Fernández C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J Neurophysiol* (1984) 51:1236–56. doi:10.1152/jn.1984.51.6.1236
8. Fitzpatrick R, Day BL. Probing the human vestibular system with galvanic stimulation. *J Appl Physiol* (2004) 96:2301–16. doi:10.1152/japplphysiol.00008.2004
9. Iwasaki S, Yamamoto Y, Togo F, Kinoshita M, Yoshifuji Y, Fujimoto C, et al. Noisy vestibular stimulation improves body balance in bilateral vestibulopathy. *Neurology* (2014) 82:969–75. doi:10.1212/wnl.0000000000000215
10. Goel R, Kofman I, Jeevarajan J, De Dios Y, Cohen H, Bloomberg J, et al. Using low levels of stochastic vestibular stimulation to improve balance function. *PLoS One* (2015) 10(8):e0136335. doi:10.1371/journal.pone.0136335
11. Wuehr M, Nusser E, Krafczyk S, Straube A, Brandt T, Jahn K, et al. Noise-enhanced vestibular input improves dynamic walking stability in healthy subjects. *Brain Stimulat* (2016) 9:109–16. doi:10.1016/j.brs.2015.08.017
12. Mulavara A, Kofman I, De Dios Y, Miller C, Peters B, Goel R, et al. Using low levels of stochastic vestibular stimulation to improve locomotor stability. *Front Syst Neurosci* (2015) 9:117. doi:10.3389/fnsys.2015.00117
13. Wuehr M, Nusser E, Decker J, Krafczyk S, Straube A, Brandt T, et al. Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy. *Neurology* (2016) 86:2196–202. doi:10.1212/wnl.0000000000002748
14. Fujimoto C, Yamamoto Y, Kamogashira T, Kinoshita M, Egami N, Uemura Y, et al. Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in elderly adults. *Sci Rep* (2016) 6:37575. doi:10.1038/srep37575
15. Samoudi G, Jivegård M, Mulavara A, Bergquist F. Effects of stochastic vestibular galvanic stimulation and LDOPA on balance and motor symptoms in patients with Parkinson's disease. *Brain Stimulat* (2015) 8:474–80. doi:10.1016/j.brs.2014.11.019
16. Lee S, Kim D, Svenkeson D, Parras G, Oishi M, McKeown M. Multifaceted effects of noisy galvanic vestibular stimulation on manual tracking behavior in Parkinson's disease. *Front Syst Neurosci* (2015) 9:5. doi:10.3389/fnsys.2015.00005
17. Pan W, Soma R, Kwak S, Yamamoto Y. Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. *J Neurol* (2008) 255:1657–61. doi:10.1007/s00415-008-0950-3
18. Wuehr M, Boerner JC, Pradhan C, Decker J, Jahn K, Brandt T, et al. Stochastic resonance in the human vestibular system – noise-induced facilitation of vestibulospinal reflexes. *Brain Stimul* (2017) 11(2):261–3. doi:10.1016/j.brs.2017.10.016
19. Priesol A, Valko Y, Merfeld D, Lewis R. Motion perception in patients with idiopathic bilateral vestibular hypofunction. *Otolaryngol Head Neck Surg* (2014) 150:1040–2. doi:10.1177/0194599814526557
20. Bacsi A, Colebatch J. Evidence for reflex and perceptual vestibular contributions to postural control. *Exp Brain Res* (2004) 160:22–8. doi:10.1007/s00221-004-1982-2
21. Mulavara A, Fiedler M, Kofman I, Wood S, Serrador J, Peters B, et al. Improving balance function using vestibular stochastic resonance: optimizing stimulus characteristics. *Exp Brain Res* (2011) 210:303–12. doi:10.1007/s00221-011-2633-z
22. Pavlik A, Inglis J, Lauk M, Oddsson L, Collins J. The effects of stochastic galvanic vestibular stimulation on human postural sway. *Exp Brain Res* (1999) 124:273–80. doi:10.1007/s002210050623
23. Day BL, Fitzpatrick RC. Virtual head rotation reveals a process of route reconstruction from human vestibular signals. *J Physiol* (2005) 567:591–7. doi:10.1113/jphysiol.2005.092544
24. Leek M. Adaptive procedures in psychophysical research. *Percept Psychophys* (2001) 63:1279–92. doi:10.3758/bf03194543
25. Shen Y. Comparing adaptive procedures for estimating the psychometric function for an auditory gap detection task. *Atten Percept Psychophys* (2013) 75:771–80. doi:10.3758/s13414-013-0438-9
26. Benson A, Spencer M, Stott J. Thresholds for the detection of the direction of whole-body, linear movement in the horizontal plane. *Aviat Space Environ Med* (1986) 57:1088–96.
27. Grabherr L, Nicoucar K, Mast F, Merfeld D. Vestibular thresholds for yaw rotation about an earth-vertical axis as a function of frequency. *Exp Brain Res* (2008) 186:677–668. doi:10.1007/s00221-008-1350-8
28. Wichmann F, Hill N. The psychometric function: I. Fitting, sampling, and goodness of fit. *Percept Psychophys* (2001) 63:1293–313. doi:10.3758/bf03194544
29. Benson A, Hutt E, Brown S. Thresholds for the perception of whole-body angular movement about a vertical axis. *Aviat Space Environ Med* (1989) 60:205–13.
30. Chaudhuri S, Karmali F, Merfeld D. Whole body motion-detection tasks can yield much lower thresholds than direction-recognition tasks: implications for the role of vibration. *J Neurophysiol* (2013) 110(12):2764–72. doi:10.1152/jn.00091.2013
31. Valko Y, Lewis R, Priesol A, Merfeld D. Vestibular labyrinth contributions to human whole-body motion discrimination. *J Neurosci* (2012) 32:13537–42. doi:10.1523/jneurosci.2157-12.2012
32. Karmali F, Lim K, Merfeld D. Visual and vestibular perceptual thresholds each demonstrate better precision at specific frequencies and also exhibit optimal integration. *J Neurophysiol* (2013) 111:2393–403. doi:10.1152/jn.00332.2013
33. Mardirossian V, Karmali F, Merfeld D. Thresholds for human perception of roll tilt motion. *Otol Neurotol* (2014) 35(5):857–60. doi:10.1097/mao.0000000000000346
34. Lim K, Karmali F, Nicoucar K, Merfeld D. Perceptual precision of passive body tilt is consistent with statistically optimal cue integration. *J Neurophysiol* (2017) 117:2037–52. doi:10.1152/jn.00073.2016
35. Dakin C, Son G, Inglis J, Blouin J. Frequency response of human vestibular reflexes characterized by stochastic stimuli. *J Physiol* (2007) 583(3):1117–27. doi:10.1113/jphysiol.2007.133264
36. Forbes P, Dakin C, Vardy A, Happee R, Siegmund G, Schouten A, et al. Frequency response of vestibular reflexes in neck, back, and lower limb muscles. *J Neurophysiol* (2013) 110(8):1869–81. doi:10.1152/jn.00196.2013
37. Haburcakova C, Lewis R, Merfeld D. Frequency dependence of vestibuloocular reflex thresholds. *J Neurophysiol* (2011) 107(3):973–83. doi:10.1152/jn.00451.2011
38. Kyriakareli A, Cousins S, Pettorossi V, Bronstein A. Effect of transcranial direct current stimulation on vestibular-ocular and vestibulo-perceptual thresholds. *Neuroreport* (2013) 24(14):808–12. doi:10.1097/wnr.0b013e3283646e65

39. Zingler V, Cnyrim C, Jahn K, Weintz E, Fernbacher J, Frenzel C, et al. Causative factors and epidemiology of bilateral vestibulopathy in 255 patients. *Ann Neurol* (2007) 61:524–32. doi:10.1002/ana.21105

40. Gillespie M, Minor L. Prognosis in bilateral vestibular hypofunction. *Laryngoscope* (1999) 109:35–41. doi:10.1097/00005537-199901000-00008

41. Iwasaki S, Karino S, Kamogashira T, Togo F, Fujimoto C, Yamamoto Y, et al. Effect of noisy galvanic vestibular stimulation on ocular vestibular-evoked myogenic potentials to bone-conducted vibration. *Front Neurol* (2017) 8:26. doi:10.3389/fneur.2017.00026

42. Grossman G, Leigh R, Abel L, Lanska D, Thurston S. Frequency and velocity of rotational head perturbations during locomotion. *Exp Brain Res* (1988) 70:470–6. doi:10.1007/bf00247595

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CM and handling Editor declared their shared affiliation.

3. Section 3

3.1. Article 2

NEUROSCIENCE
RESEARCH ARTICLE
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Noisy Galvanic Vestibular Stimulation Primarily Affects Otolith-Mediated Motion Perception

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Abstract—Noisy galvanic vestibular stimulation (nGVS) has been shown to improve vestibular perception in healthy subjects. However, it is unclear whether both the semicircular canals (SCCs) and otolith organs contribute to this enhancement or is it confined to one of these structures. To elucidate this matter, nGVS amplitudes with optimal effect on postural control were determined in 12 healthy subjects during upright stance. These amplitudes were then applied during perceptual direction-recognition tasks in inter-aural translation (otolith-mediated perception) as well as yaw rotation with the head pitched forward 71 deg (SCC-mediated perception) and compared to sham stimulation. Nine out of 12 subjects showed significantly improved direction-recognition thresholds in the inter-aural translation task during nGVS compared to sham stimulation ($p \leq 0.03$; mean threshold reduction: 38.8%). Only 6 of 12 subjects showed mild improvements in the yaw rotation task during nGVS ($p > 0.05$). In addition, elevated baseline thresholds during the inter-aural translation task significantly correlated with a larger magnitude of improvement ($R = 0.72$, $p = 0.01$). In conclusion, nGVS appears to primarily impact otolith-mediated perception while only mildly affecting the SCCs. Thus, this stimulation approach could be a complementary candidate to vestibular implants that are currently limited to SCC-mediated vestibular function.

Key words: vestibular motion perception, noisy galvanic stimulation, stochastic resonance, otoliths, semicircular canals.

INTRODUCTION

Recent studies have demonstrated that the performance of sensory systems can be enhanced by the presence of an imperceptible noise (Collins et al., 1996; Zeng et al., 2000; Moss et al., 2004; van der Groen and Wenderoth, 2016). These improvements were attributed to the mechanism of stochastic resonance (SR), in which weak incoming signals get amplified by interacting with low-intensity noise and thereby become detectable (Benzi et al., 1981; Collins et al., 1995). SR in the reflexive vestibular system has been exhibited via imperceptible noisy galvanic vestibular stimulation (nGVS) in healthy subjects and patients with bilateral vestibular loss (Iwasaki et al., 2014; Goel et al., 2015; Mulavara et al., 2015; Fujimoto et al., 2016; Wuehr et al., 2016a, b; Schniepp et al., 2018; Wuehr et al., 2018). Moreover, SR has recently been shown to improve vestibular motion perception in healthy subjects across different frequencies of passive roll-tilts (Galvan-Garza et al., 2018; Keywan et al., 2018).

Since roll-tilts activate both semicircular canals (SCCs) and otolith organs, it is, however, unclear whether one or both these structures contribute to the noise-induced improvements in vestibular perception. Various studies suggest that GVS activates both the otolith organs as well as the SCCs. Nonetheless, there seems to be a preferential activation of the otoliths by low amplitude galvanic currents, while higher current amplitudes appear to additionally activate the SCCs (Zink et al., 1997, 1998; Kim and Curthoys, 2004; Curthoys and Macdougall, 2012). Recently, nGVS has been shown to facilitate otolith-mediated oculomotor responses (Iwasaki et al., 2017; Serrador et al., 2018); however there has been no direct comparison between otolith- and SCC-mediated responses as a result of nGVS stimulation. A more detailed account on the site of action of nGVS is particularly important since this stimulation technique has been suggested as a potential rehabilitation method for patients with balance disorders (Wuehr et al., 2017). To elucidate this matter, we characterized the nGVS impact on the vestibular perceptual pathways dominated by either the SCCs and or otoliths, using two

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Abbreviations: CoP, center of pressure; MV, mean velocity; nGVS, noisy galvanic vestibular stimulation; RMS, root mean square; SCCs, semicircular canals; SR, stochastic resonance.

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separate vestibular direction-recognition tasks that allow the examination of the nGVS effect on each of these structures in isolation.

METHODS

Procedures

Ethics. The study protocol was approved by the ethics committee of the medical faculty of the Ludwig-Maximilian University of Munich. The study was conducted in conformity with the Declaration of Helsinki. Informed consents were obtained from all the study subjects prior to participation.

nGVS stimulation. nGVS was applied in 12 healthy subjects (seven males; mean age 26.8 ± 2.3 years) via a pair of Ag-AgCl electrodes attached bilaterally over the left and right mastoid process. A constant current stimulator (DS5, Digitimer, Hertfordshire, UK) delivered a zero-mean Gaussian white noise within a frequency range of 0–2 Hz (Keywan et al., 2018).

Optimal nGVS amplitude. Body sway of each subject was recorded for 30 s by a stabilometer platform (Kistler 9261A, Kistler Group, Winterthur, Switzerland) while standing on foam with eyes closed. This procedure was repeated eight times, each time with a different amplitude of nGVS, ranging from 0 to 700 μA in a randomized manner. For each trial, three parameters characterizing body sway were analyzed offline: The mean velocity (MV) and root mean square (RMS) of the center of pressure (CoP) in the anterior–posterior (AP) and medio-lateral (ML) planes as well as the envelopment area traced by the CoP movement. The ratio of each parameter during the stimulation conditions to that of the baseline condition (i.e., 0 μA) was calculated (i.e., normalized ratio). The nGVS amplitude that caused the greatest reduction in the normalized ratios of all three stance parameters (i.e., enhanced postural control) was determined as the optimal nGVS amplitude. The whole procedure was performed once with the head straight ahead (Fig. 1A), and once with the head pitched forward around 71 deg (Fig. 2A). (Cathers et al., 2005; St George and Fitzpatrick, 2011) The correct pitch angle of the head was checked by the experimenter using a protractor. Between trials, subjects had a 1-min break to alleviate any after-effects of nGVS.

Vestibular direction-recognition experiments. After ascertaining the optimal nGVS amplitudes, subjects performed direction-recognition experiments (150 trials each, 3-down 1-up paradigm) using a six-degree-of-freedom motion platform (Moog 6DOF2000E, East Aurora, New York) in two conditions to examine nGVS effect on otolith- and SCC-mediated vestibular perception in isolation: (A) head in normal position during inter-aural translations (otolith-mediated perception) at 1 Hz and (B) head pitched forward around 71 deg during yaw rotations (anterior and posterior SCC-mediated perception) at 1 Hz. During the whole procedure, the head was stabilized by padded metal-arms attached to the subject's head. Each trial consisted of a single half-cycle that follows a raised-cosine velocity profile to the right or to the left (Figs. 1C and 2C) and subjects had to indicate the direction of movement by a button press. A cumulative Gaussian distribution function was then fitted to the response data, which yielded a maximum likelihood psychometric fit. Direction-recognition tasks were used to minimize the influence of vibration and other non-directional cues on vestibulo-perceptual thresholds (Chaudhuri et al., 2013). Both conditions were performed in a randomized order for nGVS and sham stimulation (i.e., nGVS at 0 μA). Noise-canceling head-phones were used to mask incoming sound cues from the platform. All experiments were performed in total darkness with eyes closed.

Statistical analysis

Statistics were performed on the log-transformed vestibular thresholds to achieve normal distribution (Benson et al., 1986; 1989; Grabherr et al., 2008). The effect of nGVS on vestibular perceptual thresholds in each condition was determined using paired *t*-tests. Paired *t*-tests were also performed to compare optimal nGVS amplitudes obtained during the head straight vs. the head pitched postural condition. Pearson's correlations were performed to analyze relationships between baseline perceptual thresholds (i.e., during sham nGVS) and the magnitude of changes in posture and perceptual thresholds during application of nGVS at optimal amplitudes. Results were considered significant if $p < 0.05$. Statistical analysis was performed using Matlab (2017a, The Mathworks, USA).

RESULTS

All participants showed optimal nGVS amplitudes in the postural tasks during head straight (0.24 ± 0.16 μA; Fig. 1AB) and head pitched (0.34 ± 0.2 μA; Fig. 2AB) conditions. There was no significant difference between the optimal nGVS amplitudes of both conditions ($t(11) = 1.97$; $p > 0.05$; Cohen's $d = 0.6$). Furthermore, optimal nGVS amplitudes were at an imperceptible intensity for all participants. In the direction-recognition tasks, for condition A (inter-aural translation; Fig. 1C, D), 9 out of 12 subjects showed improved recognition thresholds during nGVS (mean threshold = 0.53 ± 0.07 cm/s) compared to the sham stimulation (mean threshold = 0.79 ± 0.13 cm/s) (mean reduction = 38.8 ± 0.5%; $t(11) = 2.62$; $p \leq 0.03$; Cohen's $d = 0.8$). Furthermore, greater nGVS-induced threshold reductions in the inter-aural task were correlated with higher baseline perceptual thresholds determined during sham stimulation ($R = -0.72$; $p \leq 0.010$; Fig. 1E).

For condition B (yaw rotation, Fig. 2A), 6 out of 12 subjects showed mild nGVS-induced improvements (nGVS mean threshold = 0.85 ± 0.13 deg/s; sham mean threshold = 0.85 ± 0.08 deg/s). However, the group effect was not significant ($t(11) = 0.04$; $p > 0.05$; Cohen's $d = 0.0$) (Fig. 2CD). No correlation was found between the magnitude of nGVS-induced threshold

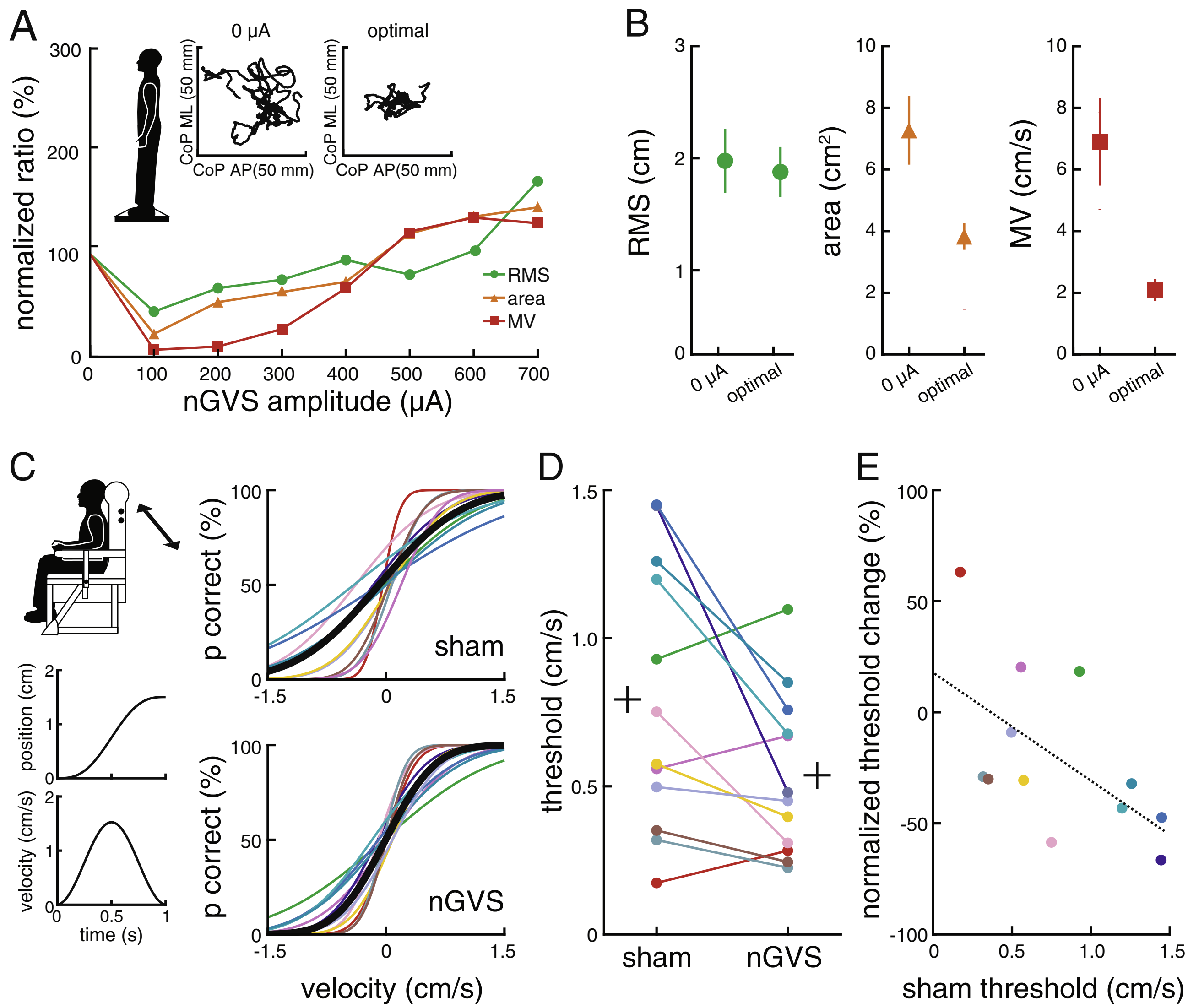

Fig. 1. Experimental conditions and main results for the inter-aural translation direction-recognition task. (A) Depiction of the postural task with head straight and exemplary nGVS balance responses exhibiting a bell-shaped response curve with maximal improvements at 100 μA. Inset: corresponding CoP trajectories during nGVS at 0 μA and optimal nGVS intensity. (B) Mean of the postural parameters during nGVS at 0 μA compared to optimal nGVS intensity. (C) Left: The optimal nGVS amplitude determined during the postural task was used during the illustrated 1-Hz inter-aural translation direction-recognition task (arrows indicate translational axis) with the depicted displacement and raised-cosine velocity profile of the motion platform. Right: Individual psychometric curves of the perceptual performance during sham compared to optimal nGVS in the inter-aural translation task (black lines represent the group average for each condition). (D) Corresponding Individual perceptual thresholds (black crosses represent the group mean for each condition). (E) Higher individual thresholds during sham condition were associated to greater nGVS-induced threshold reductions ($R = -0.72$; $p \leq 0.010$). nGVS = noisy galvanic vestibular stimulation; RMS = root mean square; MV = mean velocity; CoP = center of pressure; ML: medio-lateral; AP = anterior–posterior.

changes and vestibular thresholds at baseline (Fig. 2E). Moreover, higher or lower optimal nGVS intensities were not associated to nGVS-induced alterations in perceptual thresholds (inter-aural translation: $p > 0.05$; yaw rotation: $p > 0.05$). Finally, we did not find a correlation between noise-induced improvements in the postural and perceptual tasks, in accordance with our previous study (Keywan et al., 2018).

DISCUSSION

In this study we compared the effect of nGVS on vestibular perception during passive motion stimulations consistent with either the otoliths or SCCs activation. Our results show that nGVS primarily affects translational motion perception while mildly influencing rotational perception. Like in previous studies, those individuals with higher baseline perceptual thresholds showed greater nGVS-induced improvements (Galvan-Garza et al., 2018). This finding suggests that nGVS might be particularly beneficial for individuals with elevated thresholds for vestibular motion perception, i.e., patients with vestibular hypofunction (Priesol et al. 2014) and the elderly (Bermúdez et al. 2016). The observed nGVS effects on otolith-mediated perception are in line with previously demonstrated nGVS-induced

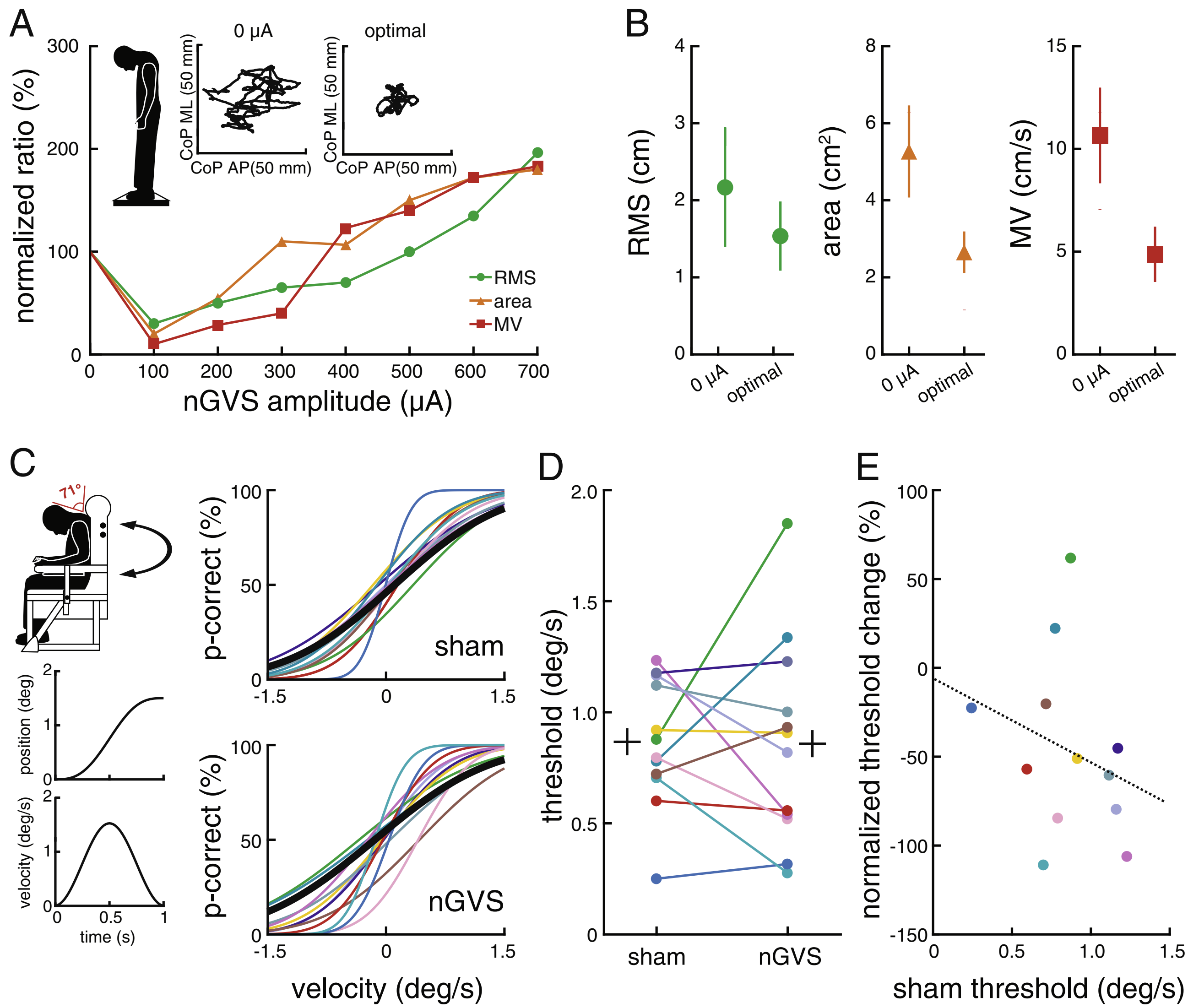

Fig. 2. Experimental conditions and main results for yaw rotation direction-recognition task. (A) Depiction of the postural task with the head inclined 71 deg and exemplary nGVS balance responses exhibiting a bell-shaped response curve with maximal improvements at 100 μA. Inset: corresponding CoP trajectories during nGVS at 0 μA and optimal nGVS intensity. (B) Mean of the postural parameters during nGVS at 0 μA compared to optimal nGVS intensity. (C) Left: The optimal nGVS amplitude determined during the postural task in (A) was used during the illustrated 1-Hz yaw rotation direction-recognition task (arrows indicate rotational axis) with the depicted displacement and raised-cosine velocity profile of the motion platform. Right: Individual psychometric curves of the perceptual performance during sham compared to optimal nGVS in the yaw rotation task (black lines represent the group average for each condition). (D) Corresponding Individual perceptual thresholds (black crosses represent the group mean for each condition). (E) Individual yaw rotation thresholds during sham condition did not correlate with nGVS-induced threshold reductions. nGVS = noisy galvanic vestibular stimulation; RMS = root mean square; MV = mean velocity; CoP = center of pressure; ML: medio-lateral; AP = anterior–posterior.

improvements in otolith-mediated ocular-motor-responses (Iwasaki et al., 2017; Serrador et al., 2018).

There is an ongoing debate regarding what GVS actually activates (Cohen et al., 2011; 2012; Curthoys and Macdougall, 2012). The current GVS model suggests that both otolith and SCC afferents are uniformly stimulated. Nonetheless, GVS at low intensities appears to primarily affect firing rates of irregular compared to regular vestibular afferents (Kim and Curthoys, 2004). Detection thresholds of vestibular afferents have been shown to be analogous to human perceptual vestibular thresholds (Yu et al., 2012). In the SCC, *regular* vestibular afferents exhibit lower thresholds and better coding for sinusoidal rotations over behaviorally relevant frequencies compared to irregular afferents (Sadeghi et al., 2007). On the contrary, in the otoliths, *irregular* rather than regular afferents have been shown to exhibit lower detection thresholds during 1-Hz sinusoidal translations (Yu et al., 2012). Therefore, given that the main carrier for rotational information processing appears to be regular afferents, which are only mildly affected by low-intensity GVS, could explain the observed minor effects of nGVS on SCC-mediated perception. In contrast, the dominance of irregular afferents – the primary activation site of low-intensity GVS – in translational motion perception, could explain the significant facilitatory effects of nGVS on otolith-mediated perception. This does not suggest that nGVS only activates otolith afferents; rather, this explanation it is based on the premise that both the otolith and SCC afferents were affected, yet due to the difference in the main information-carrier in both cases (i.e., irregular vs. regular afferents), the influence on *motion perception* by this stochastic-resonance-inducing stimulation seems to be reflected more on the otolith plane of motion.

The results of this study could be affected by at least two factors. First, we only tested one frequency of motion (1 Hz). This frequency was chosen based on our previous study, in which nGVS effects on roll-tilt perceptual thresholds were most pronounced (Keywan et al., 2018). It further represents a behaviorally relevant frequency (Grossman et al., 1988) and vestibular threshold for yaw rotations and inter-aural translations at 1 Hz are well characterized in the literature (Valko et al., 2012; Karmali et al., 2017) Nevertheless, further studies are required to examine whether more pronounced nGVS effects on SCC-mediated perception might be present at other frequencies of motion. Secondly, there is currently no consensus on the optimal frequency bandwidth of the stimulation signal used. nGVS at various bandwidths has been shown to improve vestibular function in the past, ranging from 0–2 Hz (Keywan et al., 2018) to as high as 0–640 Hz (Inukai et al., 2018). The stimulation bandwidth of 0–2 Hz was chosen in this study since it covers the natural frequencies of head movements occurring during quiet stance (Keywan et al., 2018). Currently, we cannot exclude that nGVS at broader frequency bandwidth might induce more pronounced effects on SSC-mediated function.

In conclusion, we provide first evidence that nGVS predominantly augments otolith-mediated vestibular perceptual function. This in turn could lead to more informed decisions regarding which patients might be eligible for a treatment with nGVS. Moreover, recent advances in vestibular prostheses have enabled electrical compensation for vestibular loss (Lewis et al., 2011; Merfeld and Lewis, 2012). These prostheses, however, are so far only designed to target SCC-mediated vestibular function. Our current results indicate that nGVS with its primary effect on otolith-mediated motion perception could potentially play an important complementary role to the current generation of vestibular prostheses.

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COMPETING FINANCIAL INTEREST

We declare that the authors have no competing interests as defined by Nature Publishing Group, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

REFERENCES

Benson A, Spencer M, Stott J (1986) Thresholds for the detection of the direction of whole-body, linear movement in the horizontal plane. Aviat Space Environ Med 57:1088–1096.

Benson A, Hutt E, Brown S (1989) Thresholds for the perception of whole-body angular movement about a vertical axis. Aviat Space Environ Med 60:205–213.

Benzi R, Sutera A, Vulpiani A (1981) The mechanism of stochastic resonance. J Phys A 14:L453–L457. https://doi.org/10.1088/0305-4470/14/11/006.

Bermúdez RMC, Clark TK, Wang W, Leeder T, Bian Y, Merfeld DM (2016) Vestibular perceptual thresholds increase above the age of 40. Front Neurol 7:1e17. https://doi.org/10.3389/fneur.2016.00162.

Cathers I, Day BL, Fitzpatrick RC (2005) Otolith and canal reflexes in human standing. J Physiol 563:229–234. https://doi.org/10.1113/jphysiol.2004.079525.

Chaudhuri SE, Karmali F, Merfeld DM (2013) Whole body motion-detection tasks can yield much lower thresholds than direction-recognition tasks: implications for the role of vibration. J Neurophysiol 110:2764–2772. https://doi.org/10.1152/jn.00091.2013.

Cohen B, Yakushin SB, Holstein GR (2011) What does galvanic vestibular stimulation actually activate? Front Neurol 2:90. https://doi.org/10.3389/fneur.2011.00090.

Cohen B, Yakushin SB, Holstein GR (2012) What does galvanic vestibular stimulation actually activate: response. Front Neurol 3:148. https://doi.org/10.3389/fneur.2012.00148.

Collins JJ, Chow CC, Imhoff TT (1995) Stochastic resonance without tuning. Nature 376:236–238. https://doi.org/10.1038/376236a0.

Collins JJ, Imhoff TT, Grigg P (1996) Noise-enhanced tactile sensation. Nature 383:770. https://doi.org/10.1038/383770a0.

Curthoys IS, Macdougall HG (2012) What galvanic vestibular stimulation actually activates. Front Neurol 3:117. https://doi.org/10.3389/fneur.2012.00117.

Fujimoto C et al (2016) Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in elderly adults. Scientific Reports 6:37575. https://doi.org/10.1038/srep37575.

Galvan-Garza RC, Clark TK, Mulavara AP, Oman CM (2018) Exhibition of stochastic resonance in vestibular tilt motion perception. Brain Stimul. https://doi.org/10.1016/j.brs.2018.03.017.

Goel R et al (2015) Using Low Levels of Stochastic Vestibular Stimulation to Improve Balance Function. PLoS One 10. https://doi.org/10.1371/journal.pone.0136335 e0136335.

Grabherr L, Nicoucar K, Mast F, Merfeld D (2008) Vestibular thresholds for yaw rotation about an earth-vertical axis as a function of frequency. Experimental Brain Research 186:677–768. https://doi.org/10.1007/s00221-008-1350-8.

Grossman GE, Leigh RJ, Abel LA, Lanska DJ, Thurston SE (1988) Frequency and velocity of rotational head perturbations during locomotion. Exp Brain Res 70:470–476.

Inukai Y et al (2018) Effect of noisy galvanic vestibular stimulation on center of pressure sway of static standing posture. Brain Stimul 11:85–93. https://doi.org/10.1016/j.brs.2017.10.007.

Iwasaki S, Yamamoto Y, Togo F, Kinoshita M, Yoshifuji Y, Fujimoto C, et al. (2014) Noisy vestibular stimulation improves body balance in bilateral vestibulopathy. Neurology 82:969–975. https://doi.org/10.1212/wnl.0000000000000215.

Iwasaki S et al (2017) Effect of Noisy Galvanic Vestibular Stimulation on Ocular Vestibular-Evoked Myogenic Potentials to Bone-Conducted Vibration. Front Neurol 8:26. https://doi.org/10.3389/fneur.2017.00026.

Karmali F, Bermudez Rey MC, Clark TK, Wang W, Merfeld DM (2017) Multivariate Analyses of Balance Test Performance, Vestibular Thresholds, and Age. Front Neurol 8:578. https://doi.org/10.3389/fneur.2017.00578.

Keywan A, Wuehr M, Pradhan C, Jahn K (2018) Noisy galvanic stimulation improves roll-tilt vestibular perception in healthy

subjects. Front Neurol 9:83. https://doi.org/10.3389/fneur.2018.00083.
Kim J, Curthoys IS (2004) Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetized guinea pig. Brain Res Bull 64:265–271. https://doi.org/10.1016/j.brainresbull.2004.04.016.
Lewis RF et al (2011) Vestibular prosthesis tested in rhesus monkeys. Conf Proc IEEE Eng Med Biol Soc:2277–2279. https://doi.org/10.1109/IEMBS.2011.6090573.
Merfeld DM, Lewis RF (2012) Replacing semicircular canal function with a vestibular implant. Curr Opin Otolaryngol Head Neck Surg 20:386–392. https://doi.org/10.1097/MOO.0b013e328357630f.
Moss F, Ward LM, Sannita WG (2004) Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol 115:267–281. https://doi.org/10.1016/j.clinph.2003.09.014.
Mulavara A, Kofman I, De Dios Y, Miller C, Peters B, Goel R, et al. (2015) Using low levels of stochastic vestibular stimulation to improve locomotor stability. Front Syst Neurosci 9:117. https://doi.org/10.3389/fnsys.2015.00117.
Priesol AJ, Valko Y, Merfeld DM, Lewis RF (2014) Motion perception in patients with idiopathic bilateral vestibular hypofunction. Otolaryngol Head Neck Surg 150:1040–1042.
Sadeghi SG, Chacron MJ, Taylor MC, Cullen KE (2007) Neural variability, detection thresholds, and information transmission in the vestibular system. J Neurosci 27:771–781. https://doi.org/10.1523/JNEUROSCI.4690-06.2007.
Schniepp R et al (2018) Noisy vestibular stimulation improves vestibulospinal function in patients with bilateral vestibulopathy. J Neurol. https://doi.org/10.1007/s00415-018-8814-y.
Serrador JM, Deegan BM, Geraghty MC, Wood SJ (2018) Enhancing vestibular function in the elderly with imperceptible electrical stimulation. Sci Rep 8:336. https://doi.org/10.1038/s41598-017-18653-8.
St George RJ, Fitzpatrick RC (2011) The sense of self-motion, orientation and balance explored by vestibular stimulation. J Physiol 589:807–813. https://doi.org/10.1113/jphysiol.2010.197665.
Valko Y, Lewis RF, Priesol AJ, Merfeld DM (2012) Vestibular labyrinth contributions to human whole-body motion discrimination. J Neurosci 32:13537–13542. https://doi.org/10.1523/JNEUROSCI.2157-12.2012.
van der Groen O, Wenderoth N (2016) Transcranial random noise stimulation of visual cortex: stochastic resonance enhances central mechanisms of perception. J Neurosci 36:5289–5298. https://doi.org/10.1523/JNEUROSCI.4519-15.2016.
Wuehr M, Nusser E, Decker J, Krafczyk S, Straube A, Brandt T, et al. (2016a) Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy. Neurology 86:2196–2202. https://doi.org/10.1212/wnl.0000000000002748.
Wuehr M, Nusser E, Krafczyk S, Straube A, Brandt T, Jahn K, et al. (2016b) Noise-enhanced vestibular input improves dynamic walking stability in healthy subjects. Brain Stimulation 9:109–116. https://doi.org/10.1016/j.brs.2015.08.017.
Wuehr M et al (2018) Stochastic resonance in the human vestibular system – noise-induced facilitation of vestibulospinal reflexes. Brain Stimul 11:261–263. https://doi.org/10.1016/j.brs.2017.10.016.
Wuehr M, Decker J, Schniepp R (2017) Noisy galvanic vestibular stimulation: an emerging treatment option for bilateral vestibulopathy. J Neurol 264:81–86. https://doi.org/10.1007/s00415-017-8481-4.
Yu XJ, Dickman JD, Angelaki DE (2012) Detection thresholds of macaque otolith afferents. J Neurosci 32:8306–8316. https://doi.org/10.1523/JNEUROSCI.1067-12.2012.
Zeng FG, Fu QJ, Morse R (2000) Human hearing enhanced by noise. Brain Res 869:251–255. https://doi.org/10.1016/S0006-8993(00)02475-6.
Zink R, Bucher SF, Weiss A, Brandt T, Dieterich M (1998) Effects of galvanic vestibular stimulation on otolithic and semicircular canal eye movements and perceived vertical. Electroencephalogr Clin Neurophysiol 107:200–205.
Zink R, Steddin S, Weiss A, Brandt T, Dieterich M (1997) Galvanic vestibular stimulation in humans: effects on otolith function in roll. Neurosci Lett 232:171–174.

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4 Section 4

4.1 Discussion

4.1.1 Study 1

In this study we investigated the effect of nGVS on vestibular motion perception during roll-tilts at 0.2, 0.5 and 1Hz. We found a significant facilitatory effect of nGVS on perceptual thresholds during 0.5 and 1Hz, but not during 0.2Hz. We also observed that the magnitude of postural enhancement as a result of nGVS was not correlated to the magnitude of improvement on perceptual thresholds.

In addition to the points we raised in the discussion section of the published article, other related points can be further discussed. The lack of enhancing effect of nGVS on motion perception during 0.2Hz tilts, whilst improving perception at 0.5 and 1Hz is rather an intriguing finding that could provide some insight into the tilt-translation perceptual dynamics. In the discussion part of Study 1, based on a study by (Lim et al., 2017), we speculated that a possible explanation for this frequency selectivity is that roll-tilts at 0.5 and 1Hz are predominated by SCC contributions, while at 0.2Hz there is a significant contribution of the otoliths, where the effect of the nGVS gets cancelled according to the vector summation model by Fitzpatrick and Day 2004. However, in light of our subsequent study (Study 2), where we have shown that it is rather the otoliths that are most affected at 1Hz by nGVS and not the SCCs, our speculative explanation in Study 1 as to why nGVS selectively affected 0.5 and 1Hz may need to be reconsidered.

A more intriguing explanation to this apparent selectivity may be based on the canal-otolith dynamics and their representation in the brain. The representation of sensory and body dynamics in the brain, or in other words “internal models”, are well established in the vestibular literature (Glasauer, 1992; Angelaki et al., 1999), where they have been shown to be important for vestibular perception as well vestibulo-ocular reflex function (Merfeld et al., 1999; Merfeld et al., 2005a; Merfeld et al., 2005b). Merfeld at al, 2005a have depicted that during roll-tilts (i.e. the motion stimulus we used in study 1), when the stimulus is a high-frequency shift in the gravito-inertial force, subjects are more likely to perceive the stimulus as translation rather than tilt. On the contrary, at a low frequency shift in the gravito-inertial force, the stimulus is more likely to be interpreted as a tilt. In support of this observation, Lim et al., 2017 have used Kalman-filter based internal model to investigate this relationship. They reported that the higher the frequency of the gravito-inertial shift, the more the internal model overestimates the translational component, rendering roll-tilts at higher frequencies to be perceived as translation. In relation to the outcomes of study 1, this might imply that enhancing the otolith response by nGVS at higher frequency roll-tilts could therefore pronounce the perception of the translational component, and hence the observed improvements at 0.5 and 1Hz; whereas at low frequency roll-tilts, the likelihood to perceive the stimulus as a tilt rather than translation, together with the vector-cancellation taking place in the otoliths during GVS might all contribute to the lack of perceptual enhancement at 0.2Hz.

Another interesting finding we reported in this study was that postural control and vestibular motion perception can be enhanced by the *same* nGVS amplitude. Nonetheless, we also found that the magnitude of improvement induced by nGVS is not correlated between the two modalities. There are few sources that can contribute to this finding, some of which we have discussed in the publication. Specifically, we speculated that the nGVS signal bandwidth could have affected this lack of correlation, which we based on the fact that different nGVS frequency bandwidths are in coherence with different modalities of the vestibulo-spinal response (Dakin et al., 2014). Another account for this lack-of-correlation may lie in the weighting of sensory information relevant for both tasks. In order to maintain a stable posture; vestibular, somatosensory, proprioceptive and visual information all contribute to the spatial orientation and awareness of body in space as well as self motion (Horak et al., 1994; Maurer et al., 2006). Although the visual information was absent in both the postural and perceptual tasks of our study, proprioceptive signals were absent in the perceptual task while readily present in the postural task. Therefore, it is unknown how the brain's re-weighting of this information may have contributed to the reported results.

4.1.2 Study 2

In this study, we have examined the effect of nGVS on vestibular motion perception mediated either by the SCCs or the otoliths. We have shown that nGVS applied during inter-aural translations with the head straight has significantly enhanced motion perception compared to sham. On the other hand, nGVS applied during yaw rotations with the head pitched down around 71 deg had no significant effect on this SCC-mediated perception.

Previous studies have investigated the effect of nGVS on otolith-mediated oculomotor function (Serrador et al., 2018, Iwasaki et al., 2017), where they report a direct influence of nGVS on these pathways. The results we present in study 2 have confirmed these previous reports by showing that also the otolith perceptual pathways carry the amplified vestibular signal.

Nevertheless, this finding poses a dilemma: given that GVS is known to activate both the SCCs and otoliths uniformly, why only the otoliths seem to be affected? A potential answer to this finding relies on previous reports that GVS, when presented at a low-intensity, seems to show a preferential activation of otolith afferents (Kim and Curthoys, 2004). Although this information is critical to account for these findings, it seems that it is not the mere activation of the otolith afferents that produces the effect; rather, the apparent preferential activation of GVS to *irregular* otolith afferent seems to play a decisive factor in understanding our current observations. Irregular otolith afferents have been depicted to be particularly sensitive to inter-aural translational motion with significantly lower detection thresholds compared to regular afferents during 1Hz translations (Yu et al., 2012), The SCCs on the other hand do not show this difference in detection sensitivity during yaw rotations (Yu et al., 2014); with the regular afferents demonstrated to be the main information carrier of the rotational signals (Sadeghi et al., 2007). Our results are further supported by Liu et al., 2011, who recorded neuronal activity in the parieto-insular vestibular cortex (PIVC) in response to rotation and translation. They depicted that both translation-only neurons and rotation-only neurons show a near unity gain during 1Hz inter-aural translation and yaw rotation. This means that our results cannot be explained by the dynamics of cortical neurons (i.e. pronounced central otolith gain over the SCCs as a function of frequency); rather, our results seem to reflect the enhanced dynamics of the *peripheral* otolith afferents as a result of SR, which seems to be maintained up to the cortex (i.e. enhanced perception). The selective enhancement to otolith mediated perception may not, however, be generalized to all frequencies of motion, where different neuronal dynamics may apply, especially at very low and very high frequencies.

Another interesting outcome we report in this study was the significant correlation between the elevated baseline (sham) thresholds and the magnitude of improvement induced by nGVS, where we found that the higher the baseline threshold, the larger the improvement was induced by nGVS. A corresponding observation was previously reported by Galvan-Garza et al., 2018 concerning roll-tilt motion perception, as well as for otolith-ocular reflexes by Serrador et al., 2018.

5.1.3 Implications of the results

In both studies, we have demonstrated that nGVS is a promising technique in facilitating vestibular motion perception. In Study 1 we have provided first evidence that nGVS actually improves vestibular motion perception, and that its effect, although beneficial in behaviorally-relevant frequencies, might not have a uniform effect across all frequencies. In Study 2, we have tested the nGVS effect on the SCCs and otolith in isolation, and demonstrated that it predominantly affects otolith-mediated perception. Furthermore, subjects with elevated baseline thresholds showed larger improvements as a result of the nGVS application, therefore possibly solidifying the basis for its application in patient populations.

Treating patients with vestibular disorders has long posed a challenge because of the limited tools that can be applied in this respect. Vestibular physiotherapy has been the method of choice in treating these patients, with a variety of methods being developed nowadays to alleviate patient symptoms and handicap. Amongst these methods are the vestibular implants, the vestibular counterpart of cochlear implants, where an electrode array is inserted into the SCCs to compensate for the lost function. Although promising, as verified by the eye-movement responses in behaving animals (Lewis, 2016), its application is exclusively limited to the SCCs, while not targeting the otolith organ. Therefore, given the results of Study 2, together with the previous reports that showed the clear nGVS effect on otolith-mediated pathways, nGVS may hold the potential to complement the effect of the vestibular implants.

Our results seem to further encourage the current motion for nominating nGVS as a tool for rehabilitation (Herssens and McCrum, 2019; Wuehr et al., 2017). To this end, an important question arises: In what form should nGVS be applied in order to get maximum benefits? Should the stimulation be continuously applied? Does the stimulation have a sustained effect if applied for a limited period of time? Recent research suggests that applying nGVS for 30 minutes in the healthy elderly and in patients with bilateral vestibulopathy sustainably improves postural control for at least 4 hours after the cessation of the stimulus; where they referred the underlying mechanism to drive this after-effect to neural-plasticity (Fujimoto et al., 2016; Fujimoto et al., 2018). Although this finding is interesting, it does not reconcile with the working mechanism of stochastic resonance, which requires the presence of both the signal and the noise to take an effect. Nonetheless, it might be possible that the up-regulation of vestibular information during the stimulation phase promotes central adaptation leading to enhanced postural control, similar to the effects produced by long term application of supra-threshold nGVS (Dilda et al., 2014). In fact, an EEG study (Kim et al., 2013) examining the aftereffect of sub-threshold nGVS on brain rhythms has found that it alters the synchrony patters across a broad range of frequency bands, which could represent enhanced information processing due to the stochastic facilitation. However, they also report that these aftereffects were transient and unlikely to persist for long duration, stating that the induction of synaptic plasticity could not be inferred. Intrigued by these reports, and given that we have shown in both our studies that the *same* nGVS amplitude enhances both postural and perceptual functions, we speculated whether a similar effect exists for motion perception. In a sham-controlled experiment that ran over two days for each participant, we found no prolonged effect of nGVS on vestibular motion perception, where the latter only improved when the stimulation was active (manuscript currently under review). In fact, Maheu et al., 2018 have repeated the same study conducted by Fujimoto et al., 2016, where unlike the latter study, they controlled for task-dependent learning effects and also found no sustained facilitation of nGVS. Ultimately, more experimental evidence is necessary to validate either of the results.

The potential rehabilitative use of nGVS has not been limited to its sub-threshold form that induces the SR effect. Supra-threshold nGVS has also been recently examined as a tool to enhance perceptual/cognitive processes that involve vestibular information. Weech et al., 2018 have depicted that using either supra-threshold nGVS at 2 mA or noisy mastoid vibrations, both reduced vection latency as well as simulator sickness in a virtual environment. The theory behind these achieved results is that by sending noisy signals to the brain via the vestibular system, the brain then *down-weighs* the vestibular information as being unreliable, and therefore relies more on visual and somatosensory signals, leading to reduced sensation of motion. In fact, this technique is currently being transformed into a wearable device that is based on noisy vibrations of the mastoids (Otolith labs, Washington, USA), where it is claimed to have a wide variety of applications to alleviate dizziness and disorientation (e.g. VR gaming, caloric testing etc…). While this technique might help in certain *static* conditions, applying these relatively high nGVS amplitudes during ambulation where they effectively mimic a vestibular loss, might lead to falling. Therefore, such methods cannot form an alternative to a tool that enhances the processing of vestibular signals, which are crucial during motion, particularly to vestibular patients. That said, it is possible that supra-threshold nGVS could indeed be helpful in static conditions when subjects feel disoriented in surroundings where vestibular information is re-weighted (e.g. sea travel) leading to motion sickness, or during static VR gaming.

5.1.4 Limitations and future work

Although we have shown that nGVS can positively affect motion perception, it is important to bear in mind that the outcomes of these two studies represent data from a healthy population. Understanding the nature by which nGVS affects the healthy vestibular motion perception is of paramount importance; however, the perceptual dynamics of a diseased vestibular system may not fully resemble the healthy one. Therefore, we cannot exclude an effect of nGVS on patients at low frequency motion or on the SCCs. Another potential limitation of our studies was the determination of the optimal nGVS amplitudes using a posturography task. In spite the fact that those postural optimal amplitudes proved efficient in inducing improvement in vestibular perception, there was a lack of correlation between the magnitudes of improvements observed in the two modalities. Therefore, it may be possible that if optimal nGVS intensities were determined using a perceptual task rather than postural, different optimal intensities would be observed. This in turn could have also yielded positive outcomes where we reported negative ones (e.g. lack of effect at 0.2Hz in study 1, and a non-significant effect on SCCs in study 2). However, basing the optimal nGVS determination on a perceptual task that requires a large number of repetitions to produce a meaningful result holds the risk of, as stated in Study 1, not differentiating the true effect of nGVS from statistical variations induced by the repeated testing. A potential solution to this problem could be the utilization of the *adaptive stochastic resonance* approach (Mitaim et al., 2004; Krauss et al., 2017), whereby the sensory system learns to adapt its own optimal noise level that causes performance enhancement. Although promising and potentially highly important for a technology-driven rehabilitation device, the adaptive SR method has only been tested on highly controlled systems and on computer simulations, where a thorough examination of its applicability with human subjects is still lacking. Another limitation of our studies, which also extends to other studies that investigate the effect of SR on vestibular-mediated functions, is the lack of common parameters used in the stimulation signals such as frequency bandwidth. This is not unusual given the early stage of exploring the nature of nGVS effect on the normal and diseased vestibular systems; but ultimately there needs to be a consensus on the parameters that achieve the optimal outcomes.

The emergence of nGVS as potential therapeutic tool in patients with vestibular disorders necessitates the continuation of the investigative work in few domains:

1- *Perceptual-function*: work has to carry on unraveling the effect of nGVS on different rotational and translational planes in various frequencies of motion in healthy subjects. Yet more importantly, this work has to also extend to patients with vestibular disorders whom might benefit from this intervention, such as patients with bilateral vestibulopathy, persistent postural-perceptual dizziness (PPPD) and others.

2-Reflexive-function: There are many well-established laboratory tests for vestibular reflexive function such as the caloric test, Head-thrust test, vestibular-evoked myogenic potentials and others, which provide controlled stimulation to the vestibular system. These tests might be suitable to evaluate the effects of nGVS on vestibular-reflexive functions in specific patient groups.

3-*Rehabilitation*: Based on the outcomes produced by our as well as other studies that contributed to the field, it is now necessary to evaluate whether nGVS-improvements of vestibular function yield a real a real benefit on patients' daily mobility in real life. This of course demands the execution of randomized clinical trials that are designed to evaluate and monitor the immediate and long term effects of nGVS on their vestibular reflexive and perceptual functions as well as handicap.

5.1.5 Conclusion

We have shown that nGVS, facilitated by SR, can extend the dynamic range of the human vestibular perceptual system. This was demonstrated over a behaviorally-relevant frequency range (0.5 and 1Hz), with absent effect in the low frequency range of 0.2 Hz during upright roll-tilts. Further, the main contributor to the enhanced vestibular motion perception was shown to be the otolith organs, with larger improvements observed in subjects with elevated baseline vestibular thresholds. These results, together with the previous reports on nGVS effects of posture and gait, appear to hold the potential to become a valuable tool in vestibular rehabilitation.

6 References

1- Angelaki DE, McHenry MQ, Dickman JD, Newlands SD, Hess BJ. Computation of inertial motion: neural strategies to resolve ambiguous otolith information. J Neurosci. 1999;19(1):316-27.

2- Bent LR, Bolton PS, Macefield VG. Modulation of muscle sympathetic bursts by sinusoidal galvanic vestibular stimulation in human subjects. Experimental brain research. 2006;174(4):701-11.

3- Bisdorff A, Bosser G, Gueguen R, Perrin P. The epidemiology of vertigo, dizziness, and unsteadiness and its links to co-morbidities. Frontiers in neurology. 2013;4:29.

4- Cathers I, Day BL, Fitzpatrick RC. Otolith and canal reflexes in human standing. The Journal of physiology. 2005;563(Pt 1):229-34.

5- Collins JJ, Chow CC, Imhoff TT. Stochastic resonance without tuning. Nature. 1995;376(6537):236-8.

6- Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. Nature. 1996;383(6603):770.

7- Curthoys IS, Macdougall HG. What galvanic vestibular stimulation actually activates. Frontiers in neurology. 2012;3:117.

8- Dakin CJ, Luu BL, van den Doel K, Inglis JT, Blouin JS. Frequency-specific modulation of vestibular-evoked sway responses in humans. Journal of neurophysiology. 2010;103(2):1048-56.

9- Dakin CJ, Son GM, Inglis JT, Blouin JS. Frequency response of human vestibular reflexes characterized by stochastic stimuli. The Journal of physiology. 2007;583(Pt 3):1117-27.

10- Day BL, Cole J. Vestibular-evoked postural responses in the absence of somatosensory information. Brain : a journal of neurology. 2002;125(Pt 9):2081-8.

11- Dilda V, Morris TR, Yungher DA, MacDougall HG, Moore ST. Central adaptation to repeated galvanic vestibular stimulation: implications for pre-flight astronaut training. PloS one. 2014;9(11):e112131.

12- Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. Journal of applied physiology (Bethesda, Md : 1985). 2004;96(6):2301-16.

13- Forbes PA, Siegmund GP, Schouten AC, Blouin JS. Task, muscle and frequency dependent vestibular control of posture. Frontiers in integrative neuroscience. 2014;8:94.

14- Fujimoto C, Egami N, Kawahara T, Uemura Y, Yamamoto Y, Yamasoba T, et al. Noisy Galvanic Vestibular Stimulation Sustainably Improves Posture in Bilateral Vestibulopathy. Frontiers in neurology. 2018;9:900.

15- Fujimoto C, Yamamoto Y, Kamogashira T, Kinoshita M, Egami N, Uemura Y, et al. Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in elderly adults. Scientific reports. 2016;6:37575.

16- Galvan-Garza RC, Clark TK, Mulavara AP, Oman CM. Exhibition of stochastic resonance in vestibular tilt motion perception. Brain stimulation. 2018;11(4):716-22.

17- Gensberger KD, Kaufmann AK, Dietrich H, Branoner F, Banchi R, Chagnaud BP, et al. Galvanic Vestibular Stimulation: Cellular Substrates and Response Patterns of Neurons in the Vestibulo-Ocular Network. J Neurosci. 2016;36(35):9097-110.

18- Glasauer S. Interaction of semicircular canals and otoliths in the processing structure of the subjective zenith. Annals of the New York Academy of Sciences. 1992;656:847-9.

19- Goel R, Kofman I, Jeevarajan J, De Dios Y, Cohen HS, Bloomberg JJ, et al. Using Low Levels of Stochastic Vestibular Stimulation to Improve Balance Function. PloS one. 2015;10(8):e0136335.

20- Goel R, Rosenberg MJ, Cohen HS, Bloomberg JJ, Mulavara AP. Calibrating balance perturbation using electrical stimulation of the vestibular system. Journal of neuroscience methods. 2019;311:193-9.

21- Goldberg JM, Smith CE, Fernandez C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. Journal of neurophysiology. 1984;51(6):1236-56.

22- Horak FB, Shupert CL, Dietz V, Horstmann G. Vestibular and somatosensory contributions to responses to head and body displacements in stance. Experimental brain research. 1994;100(1):93-106.

23- Iwasaki S, Karino S, Kamogashira T, Togo F, Fujimoto C, Yamamoto Y, et al. Effect of Noisy Galvanic Vestibular Stimulation on Ocular Vestibular-Evoked Myogenic Potentials to Bone-Conducted Vibration. Frontiers in neurology. 2017;8:26.

24- Kim DJ, Yogendrakumar V, Chiang J, Ty E, Wang ZJ, McKeown MJ. Noisy galvanic vestibular stimulation modulates the amplitude of EEG synchrony patterns. PloS one. 2013;8(7):e69055.

25- Kim DJ, Yogendrakumar V, Chiang J, Ty E, Wang ZJ, McKeown MJ. Noisy galvanic vestibular stimulation modulates the amplitude of EEG synchrony patterns. PloS one. 2013;8(7):e69055.

26- Kim J, Curthoys IS. Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetised guinea pig. Brain research bulletin. 2004;64(3):265-71.

27- Krauss P, Metzner C, Schilling A, Schutz C, Tziridis K, Fabry B, et al. Adaptive stochastic resonance for unknown and variable input signals. Scientific reports. 2017;7(1):2450.

28- Lewis RF. Vestibular implants studied in animal models: clinical and scientific implications. Journal of neurophysiology. 2016;116(6):2777-88.

29-Lim K, Karmali F, Nicoucar K, Merfeld DM. Perceptual precision of passive body tilt is consistent with statistically optimal cue integration. Journal of neurophysiology. 2017;117(5):2037-52.

30- Liu S, Dickman JD, Angelaki DE. Response dynamics and tilt versus translation discrimination in parietoinsular vestibular cortex. Cerebral cortex (New York, NY : 1991). 2011;21(3):563-73.

31-Lund S, Broberg C. Effects of different head positions on postural sway in man induced by a reproducible vestibular error signal. Acta physiologica Scandinavica. 1983;117(2):307-9.

32-Maurer C, Mergner T, Peterka RJ. Multisensory control of human upright stance. Experimental brain research. 2006;171(2):231-50.

33-Merfeld DM, Park S, Gianna-Poulin C, Black FO, Wood S. Vestibular perception and action employ qualitatively different mechanisms. I. Frequency response of VOR and perceptual responses during Translation and Tilt. Journal of neurophysiology. 2005;94(1):186-98.

34- Merfeld DM, Park S, Gianna-Poulin C, Black FO, Wood S. Vestibular perception and action employ qualitatively different mechanisms. II. VOR and perceptual responses during combined Tilt&Translation. Journal of neurophysiology. 2005;94(1):199-205.

35- Merfeld DM, Zupan L, Peterka RJ. Humans use internal models to estimate gravity and linear acceleration. Nature. 1999;398(6728):615-8.

36-Mian OS, Dakin CJ, Blouin JS, Fitzpatrick RC, Day BL. Lack of otolith involvement in balance responses evoked by mastoid electrical stimulation. The Journal of physiology. 2010;588(Pt 22):4441-51.

37- Mitaim S, Kosko B. Adaptive stochastic resonance in noisy neurons based on mutual information. IEEE transactions on neural networks. 2004;15(6):1526-40.

38- Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2004;115(2):267-81.

39-Mulavara AP, Fiedler MJ, Kofman IS, Wood SJ, Serrador JM, Peters B, et al. Improving balance function using vestibular stochastic resonance: optimizing stimulus characteristics. Experimental brain research. 2011;210(2):303-12.

40-Pavlik AE, Inglis JT, Lauk M, Oddsson L, Collins JJ. The effects of stochastic galvanic vestibular stimulation on human postural sway. Experimental brain research. 1999;124(3):273-80.

41- Peters RM, Rasman BG, Inglis JT, Blouin JS. Gain and phase of perceived virtual rotation evoked by electrical vestibular stimuli. Journal of neurophysiology. 2015;114(1):264-73.

42-Sadeghi SG, Chacron MJ, Taylor MC, Cullen KE. Neural variability, detection thresholds, and information transmission in the vestibular system. J Neurosci. 2007;27(4):771-81.

43-Schneider E, Bartl K, Glasauer S. Galvanic vestibular stimulation combines with Earth-horizontal rotation in roll to induce the illusion of translation. Annals of the New York Academy of Sciences. 2009;1164:116-8.

44- Serrador JM, Deegan BM, Geraghty MC, Wood SJ. Enhancing vestibular function in the elderly with imperceptible electrical stimulation. Scientific reports. 2018;8(1):336.

45-St George RJ, Day BL, Fitzpatrick RC. Adaptation of vestibular signals for self-motion perception. The Journal of physiology. 2011;589(Pt 4):843-53.

46- St George RJ, Fitzpatrick RC. The sense of self-motion, orientation and balance explored by vestibular stimulation. The Journal of physiology. 2011;589(Pt 4):807-13.

47- van der Groen O, Wenderoth N. Transcranial Random Noise Stimulation of Visual Cortex: Stochastic Resonance Enhances Central Mechanisms of Perception. J Neurosci. 2016;36(19):5289-98.

48- Weech S, Moon J, Troje NF. Influence of bone-conducted vibration on simulator sickness in virtual reality. PloS one. 2018;13(3):e0194137.

49-Wuehr M, Decker J, Schniepp R. Noisy galvanic vestibular stimulation: an emerging treatment option for bilateral vestibulopathy. Journal of neurology. 2017;264(Suppl 1):81-6.

50- Wuehr M, Nusser E, Decker J, Krafczyk S, Straube A, Brandt T, et al. Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy. Neurology. 2016;86(23):2196-202.

51-Wuehr M, Nusser E, Krafczyk S, Straube A, Brandt T, Jahn K, et al. Noise-Enhanced Vestibular Input Improves Dynamic Walking Stability in Healthy Subjects. Brain stimulation. 2016;9(1):109-16.

52-Yu XJ, Dickman JD, Angelaki DE. Detection thresholds of macaque otolith afferents. J Neurosci. 2012;32(24):8306-16.

53-Yu XJ, Thomassen JS, Dickman JD, Newlands SD, Angelaki DE. Long-term deficits in motion detection thresholds and spike count variability after unilateral vestibular lesion. Journal of neurophysiology. 2014;112(4):870-89.

54- Zeng FG, Fu QJ, Morse R. Human hearing enhanced by noise. Brain Res. 2000;869(1-2):251-5.

55- Zink R, Bucher SF, Weiss A, Brandt T, Dieterich M. Effects of galvanic vestibular stimulation on otolithic and semicircular canal eye movements and perceived vertical. Electroencephalography and clinical neurophysiology. 1998;107(3):200-5.

7 Supplementary material

Author contribution

1-Keywan A, Wuehr M, Pradhan C, Jahn K. (2018) Noisy galvanic stimulation improves rolltilt vestibular perception in healthy subjects. *Front Neurol 9:83*

A.K, M.W and K.J designed the study. **A.K** incorporated the multi-frequency investigation into the study. **A.K** wrote MATLAB scripts for postural data acquisition, postural data analysis, psychophysical data acquisition, psychophysical data analysis. M.W provided MATLAB-based equations for the analysis of postural parameters. C.P assembled hardware for the Galvanic measurement. **A.K**, M.W performed statistical analysis. **A.K** created the figures. M.W adjusted the figures. **A.K** wrote the manuscript. **A.K**, M.W and K.J reviewed the manuscript and approved the final version.

2- Keywan, A., Jahn, K. & Wuehr, M. Noisy galvanic vestibular stimulation primarily affects Otolith-mediated motion perception. *Neuroscience 399, 161-166*

A.K, M.W and K.J designed the study. **A.K** incorporated the condition to measure semicircular canal's contribution in isolation. **A.K** wrote MATLAB scripts for postural data acquisition, postural data analysis, psychophysical data acquisition, psychophysical data analysis. M.W provided MATLAB-based equations for the analysis of postural parameters. **A.K**, M.W performed statistical analysis. **A.K** created the figures. M.W adjusted the figures. **A.K** wrote the manuscript. **A.K**, M.W and K.J reviewed the manuscript and approved the final version.

Affidavit

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Munich, 12/11/2019
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Effects on Posture and Perception.

is congruent with the printed version both in content and format.

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Signature doctoral candidate

7.4 Publications

1-Keywan A, Wuehr M, Pradhan C, Jahn K (2018). Noisy galvanic stimulation improves roll-tilt vestibular perception in healthy subjects. *Front Neurol* 9:83

2-Keywan, A., Jahn, K. & Wuehr M (2019). Noisy galvanic vestibular stimulation primarily affects Otolith-mediated motion perception. *Neuroscience* **399**, 161–166